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Past Asthma Exacerbation in Children Predicting Future Exacerbation: A Systematic Review

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ABBREVIATIONS

- AOR – adjusted odds ratio
- ATS – American Thoracic Society
- AUH – Aarhus University Prescription Database
- BTS – British Thoracic Society
- CAMP – Childhood Asthma Management Program
- CI – confidence intervals
- CPRD – Clinical Practice Research Datalink
- ED – Emergency Department
- EPHPP – Effective Public Health Practice Project
- ERS – European Respiratory Society
- FEV1 – forced expiratory volume in 1 second
- GINA – Global Initiative for Asthma
- HEDIS – Healthcare Effectiveness Data and Information Set
- HR – hazard ratio
- HSD – Health Search Database
- ICS – inhaled corticosteroids
- IPCI – Integrated Primary Care Information
- Mg – milligram
- n/a – not applicable
- NICE – The National Institute for Health and Care Excellence
- OCS – oral corticosteroids
- OR – odds ratio

- PACT – Pediatric Asthma Controller Trial
- PICU – Paediatric Intensive Care Unit
- PPV – positive predictive value
- PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-Analyses
- RCT – randomised controlled trial
- RL – Rachel Lowden
- RR – relative risk
- SARA – Study of Acid Reflux in Adults with Asthma
- SARCA – Study of Acid Reflux in Children with Asthma
- SIDIAP – Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària
- SIGN – Scottish Intercollegiate Guidelines Network
- TENOR – The Epidemiology and Natural History of Asthma
- UK – United Kingdom
- USA – United States of America

ABSTRACT

Acute exacerbations are common in children and potentially preventable. Currently a past exacerbation is the best predictor of a future exacerbation. We undertook a systematic review of the literature describing the relationship between past and future exacerbations. Our analysis considered whether the odds ratio (OR) for one exacerbation to predict a recurrence were different across different categories of exacerbation.

Four databases were systematically searched (MEDLINE, EMBASE, CINAHL and PsycInfo). Exacerbations were categorised by severity as: presentation to Emergency Department (ED) visit; hospital admission; Paediatric Intensive Care Unit (PICU) admission and "unspecified severity" (i.e. no distinction between severity categories was made). Meta-analysis was performed for studies where sufficient data was provided for inclusion .

There were 26 eligible articles from 9185 identified. There was significant heterogeneity in duration of follow-up, healthcare system and exacerbation definition between studies. For the unspecified severity definition, the OR for an exacerbation after a previous exacerbation was 9.87 [95% CI 5.02, 19.39] (six studies, 162,583 individuals). PICU admission was also associated with increased risk of future admission (OR 5.87 [95% CI 2.96, 11.64], two studies, 730 individuals). Meta-analysis was not possible for ED visits or hospitalisation. The median OR (range) for past ED visit predicting future ED visit was 6.27 (3.3-8.26) and for past hospitalisation predicting future hospitalisation was 3.37 (1.89-5.36).

The odds for a second asthma exacerbation do not necessarily increase with increasing severity of an initial exacerbation.

INTRODUCTION

Asthma affects over one million children in the United Kingdom (UK) (1) and over five million in the United States of America (USA) (2), making it the most common long-term medical condition in young people. Patients with asthma can experience acute exacerbations, defined by the International Consensus on Paediatric Asthma as an acute or subacute episode of progressive increase in asthma symptoms, associated with airflow obstruction (3). Exacerbations result in significant morbidity and socio-educational cost for the child through hospital admissions, interruption to education and social development, adverse effects from treatment, and a decline in lung function (4,5). Moreover, there is economic impact on caregivers through working day and productivity loss (6).

A key goal of asthma treatment is to reduce risk of exacerbations. There has been limited systematic appraisal of the literature describing whether an exacerbation is followed by a subsequent exacerbation. The Global Initiative for Asthma (GINA), the British Thoracic Society (BTS)/ Scottish Intercollegiate Guidelines Network (SIGN) and the National Institute for Clinical Excellence (NICE) guidelines highlight the importance of identifying children who are at increased risk of exacerbations, and all cite a previous exacerbation as the major risk factor (7-9). One systematic review which considered all risk factors for exacerbations in children with asthma identified 11 studies exploring previous exacerbation as a risk factor, and concluded that the odds ratio (OR) for an exacerbation being followed by a second exacerbation varied between 2.1-4.1 (10).

Here we describe a systematic review which was designed with a focus on exacerbation as a predictor of future exacerbation in children. Our hypothesis was the OR (or a positive predictive value (PPV) for case-only populations) for an exacerbation would be greater following a more severe “index” exacerbation. Meta-analysis was carried out for studies where sufficient data was provided for inclusion.

METHODS

Eligibility Criteria and Information Sources

Full papers published in English from 2000 onwards describing asthma exacerbations in children where the mean age was between five and 18 years were eligible. Studies published before 2000 were ineligible since they were considered less relevant to modern asthma care. Under five-year-olds were ineligible due to the potential to confuse an asthma exacerbation with lower respiratory tract infection in younger children. In papers where participants were of a wider age range than the desired population, if the mean age was between five and 18 years, or the desired age group of this review was reported separately, then the paper was included. Observational studies (including those using routinely acquired healthcare data and case-control and case-only studies), retrospective case-control studies and randomised controlled trials (RCT) were eligible. Data from RCT were included were included regardless of the presentation of the results and whether the intervention may have influenced these. Letters and abstracts were ineligible. The outcome was exacerbation and was reported as OR since this is the best indicator of performance (11). To make the best use of the data available (i.e. include data from case-only studies) and acknowledging OR may have limitations (12), PPV was also reported for all studies with available data.

Literature was searched on 11th January 2021 using these databases: MEDLINE, EMBASE, CINAHL and PsycInfo. Additional studies were identified from reviewing the references of the full papers assessed after the database search, including a previous review (10).

Search Strategy

The search strategy was centred around the terms 'asthma', 'asthma exacerbation/attack', 'child' and 'risk factor' and appropriate derivatives and synonyms were included. These terms were decided upon after a review of terms used in another systematic review published in this research area (10) as well as discussion with an Information Assistant. The full search strategy can be found in the supplement.

Duplicate titles were removed. Papers were screened independently, initially by title and abstract and then by full paper by one researcher (RL). Decision making was reviewed at regular meetings with the second author.

Relevant data were extracted using a pre-designed template (Table I) and included: publication date, study design, nation, study setting, data collection period, population/inclusion criteria, sample size, definition of acute exacerbation and results. For papers which did not report the required data for meta-analysis, authors were contacted and asked to provide additional data.

Study Risk of Bias Assessment

The Effective Public Health Practice Project (EPHPP) quality assessment tool for quantitative studies (13) was used to assess each individual study in terms of potential biases and global study quality. Studies are given a global rating of either strong, moderate or weak, based on their scoring in the first six domains. The tool was adapted to remove the domains blinding, intervention integrity and analyses, as these were not

relevant to the design of studies evaluated in this review. This left the following domains: selection bias, study design, confounders, data collection methods and withdrawals and drop-outs. This assessment was carried out by one author (RL) with discussion undertaken with the second author. The supplement includes explanations for how the tool was applied.

Effect Measures

The primary outcome was presence of an acute exacerbation as measured by binary (yes/no) response.

Meta-Analysis

When OR were available, meta-analysis was performed using Review Manager v5.4 software (14).

Other Synthesis Methods

Publication bias was explored using funnel plots. Exacerbations were categorised into three severity categories: presentation to emergency department (ED); admitted to hospital; admitted to paediatric intensive care unit (PICU). A fourth category of "unspecified severity" was used for remaining studies which did not distinguish between severity of exacerbation. The index exacerbation was defined as the first exacerbation in all studies. The subsequent exacerbation was defined as the exacerbation that occurred after the index exacerbation. PPVs were collectively described as a median and range. Subgroups based on study design and location of publication were created post hoc and

analyses performed to explore potential reasons for heterogeneity between the study results. The review methodology was not registered. A protocol is available on request to the corresponding author.

RESULTS

Study Selection and Study Characteristics

The initial database search identified 9185 potential titles. Figure 1 summarises the full selection process. After deletion of duplicates and screening by title and abstract, 32 full papers were reviewed of which 19 were eligible. An additional seven papers were identified after reading citations, including four in the previous review (10) meaning that 26 papers were finally included. Four of the 11 papers in the previous review (10) were excluded due to their cross-sectional nature (n=2); using the same dataset used in another included paper (n=1); and the full paper not being accessible (n=1).

Key characteristics are presented in Table I. Eleven studies were published between 2000-2010 (15-25) and 15 between 2011-2021 (26-40). 18 studies were from North America (15-25,30-34,39,40), three were from the Netherlands (27,28,37), and one each were from the UK (36), Saudi Arabia (26), Brazil (29), Thailand (38) and Australia (35).

Five studies had a prospective cohort design (15,16,18,21,24), with follow-up of two weeks (15), six months (21,24), 12 months (16) and three years (18). Ten studies used routinely acquired data (19,23,25,27,28,31,32,34,36,40), six had a retrospective case-control design (22,26,29,30,37,38) and one other (35). Data from four RCTs (17,20,33,39) were used, with follow-up of 28 days (20), 24 weeks (33), 48 weeks (17,20,33,39) and 4 years (39). In two RCTs the intervention had no effect on exacerbation outcomes and

data from both arms of the trial were pooled (20,33). The intervention in two RCTs may have influenced exacerbation outcome (17,39).

The age range for populations varied: four included children aged 2-17 years (15,21,24,32), two included 5-12 years (36,39), 19 had different age ranges spanning from 0-21 years and one did not specify paediatric participant's age (37). Unpublished data were provided by authors of two studies (17,28), with one of these providing data from six populations (28). The sample size varied from 76 (38) to 212,060 participants (28)

Risk of Bias in Studies

A summary of the quality assessment undertaken using the EPHPP Quality Assessment Tool is presented in Table II. 23 studies received a strong (15,17,19-32,34-40), three received a moderate (16,18,33) and none received a weak global rating.

Definition of Exacerbation Used

Nine studies had an unspecified severity for the index exacerbation (17,18,24,27,28,33,36,39,40), three used ED visit (13,30,32), four used hospital admission (16,22,25,31), and two used PICU for the index exacerbation (35,37). Figure 2 shows the number of studies which relate these different categories of exacerbations at baseline to risk of future exacerbations. Additionally, two studies used either ED visit or hospital admission (19,23), one used PICU or hospital admission (26) and one looked at PICU, hospital admission or ED visit (30). Other studies used definitions of exacerbation as "appropriate signs and symptoms in a known asthmatic" (21), "sudden worsening of symptoms resulting in difficulty breathing often requiring extra medicine to relieve

symptoms, with/without unscheduled ED/doctor visit" (24) and "acute asthma that was severe or did not improve after three doses of bronchodilator nebulisation" (38).

Nine studies were included where the severity of the index exacerbation was not specified (17,18,24,27,28,33,36,39,40) and OR for meta-analysis were reported in six (including 10 populations and 162,583 individuals). The pooled OR (95% Confidence interval (CI)) for an index exacerbation having a subsequent exacerbation was 9.87 (5.02, 19.39) (Figure 3). A funnel plot was asymmetric (Supplemental Figure 1).

Eight studies were identified where the index exacerbation required an ED visit (15,19,22,24,25,29,32,34). Two studies identified an association between an ED visit for asthma and a future exacerbation, using an unspecified severity definition (15,29) and three studies reported that children with an ED visit for asthma were at risk of a future hospitalisation for asthma (22,25,32). Five studies assessed the link between a past ED visit for asthma and the risk of a future visit to the ED (19,24,25,32,34). Raw data were not available to allow meta-analysis (e.g. only OR were reported). The OR for the three studies with available data (970 individuals) were 3.30, 6.27 and 8.26 (19,24,25) (Table III). The PPV for the two studies with available data were 0.12 and 0.22 (24,34).

Nine studies were identified where the index exacerbation was a hospital admission (16,19,22,23,30-32,35,37), including six which described the relationship between an index and subsequent hospital admission for asthma (16,22,23,31,32,35). The median and range of OR was 3.60 (1.89-5.36) for the five studies with available data (41,475

individuals) (16,22,23,31,35) (Table III). The PPV for the two case-only studies with available data were 0.17 and 0.69 (16,31).

Table III shows the results of two studies which looked at prior hospitalisation for asthma predicting future ED use for asthma. Three studies found an association between hospitalisation for asthma and future PICU admission with data from two studies (639 individuals) available for meta-analysis with the OR being 8.68 [95% CI 4.42, 17.07] (Figure 4, panel A).

Four studies were identified where the index exacerbation was a PICU admission (22,26,35,38). Two studies assessed the link between index and subsequent PICU admissions and the OR from meta-analysis was 5.87 [95% CI 2.96, 11.64] (26,35) (Figure 4, panel B). Two other studies reported a link between a history of PICU admission for asthma and subsequent hospitalisation with the reported OR being 2.18 (22) and 29.62 (38) (Table III).

Factors Associated with Heterogeneity

Recognising the heterogeneity in results within different exacerbation definitions we explored post hoc whether heterogeneity was reduced when subgrouping by healthcare system (i.e. North American versus other). Of the 11 studies with available data for inclusion in a meta-analysis, the OR for an index exacerbation to have a subsequent exacerbation was 2.69 [95% CI 2.19, 3.30, I-squared 49%] in the four published from

North America (15,17,33,39) (Figure 4, panel C), and 12.36 [95% CI 7.33, 20.84, I-squared 95%] for the seven published outside North America (26-29,35-37) (Figure 4, panel D). The asthma severity was not specified in three of the four studies (17,33,39) from North America and four of the seven studies from other regions (27-29,36).

We also explored whether results differed by study methodology (i.e. RCTs, prospective cohort, routinely acquired data and retrospective case-control). Where more than one exacerbation category was reported we deferred to the one with highest incidence. The median (range) of PPV differed by study design as follows: for three RCTs (17,33,39) 0.58 (0.42-0.77); for four prospective cohort studies (15,16,21,24) 0.31 (0.14-0.54); for six studies analysing routinely acquired data (25,27,28,31,34,36) 0.16 (0.06-0.43) and for four retrospective case-control studies (26,29,37,38) 0.50 (0.25-0.78) (Supplemental Table I). Across different study design there was an even distribution of exacerbation severity definitions.

Two papers reported how the risk of experiencing a future exacerbation increased over time after the index exacerbation, however this increase plateaued after three months in a study of exacerbations requiring hospitalisation (31) and after six months in another study using the unspecified severity definition (27).

DISCUSSION

Our main finding was that although as previously reported, an asthma exacerbation is a risk factor for a further exacerbation, there was no evidence of a relationship between increasing severity of an index asthma exacerbation and increasing OR for a subsequent exacerbation. Additional findings were that OR for a second exacerbation differed by geography (i.e. North America compared to other continents), study methodology (i.e. RCT and retrospective case-only study compared to cohort and routinely acquired data) and duration since index exacerbation. These findings give insight into the complexity of the relationship between index and subsequent asthma exacerbations. When speaking to parents and patients, clinicians should be aware that "mild" and "severe" initial exacerbations may both have equal OR for a subsequent exacerbation.

A previous review with a broader remit than ours has reported how an exacerbation is associated with increased OR for a future exacerbation in children (10). In our review we included a larger number of studies and in addition to confirm the earlier report (10), we find a greater magnitude of association than the earlier review for an index exacerbation being followed by a subsequent exacerbation.

In adults, the best predictor of a future exacerbation is also a past exacerbation (41), but in adults (unlike our findings in children) the OR of a future exacerbation are highest in those with history of a severe exacerbation (41). We were able to confirm in children the

observation made in adults, that the risk of further exacerbation is highest in the period following the index exacerbation, although in adults this appears to remain over a period of years, whereas in children the risk may reach a plateau after a period of months. Differences between asthma in children and adults are well described (42), so discordant findings between exacerbation risk in children and adults is expected. These findings also highlight the importance of inclusion of previous exacerbation in risk stratification models for future exacerbation.

There are some limitations to the literature which should be considered. First, there was little standardisation of the definition of exacerbation between studies, e.g. criteria for ED presentation or hospital/PICU admission were not prespecified, and this will have introduced variability into the relationship between past and future exacerbations. The OR and PPV for a second ED presentation or hospital admission were not different and this may be due to children with similar exacerbation severities entering different pathways of care in different healthcare systems, for example those in North America compared to other countries.

A second limitation was that data from 15 of the studies could not be included in the meta-analysis due to either raw data not being available or insufficient details given. An additional limitation was that the meta-analysis used raw data and could not adjust for factors which may have differed between groups with and without an exacerbation (e.g. gender, age, race, severity of asthma, or month of exacerbation) and the magnitude of the actual OR may differ from that reported herein. A further limitation is that none of

the studies considered the cause of the exacerbation nor described different outcomes for different triggers. Therefore we cannot comment whether different triggers are associated with different risk for future exacerbations and therefore risk assessment should consider whether causes of exacerbation could be avoided. Additionally, details of the treatment that children received, both for acute symptoms and asthma prevention, were not provided. Adherence to preventer therapy was also not considered. Lack of adequate asthma preventer treatment and/or lack of adherence to asthma preventer treatment are both important risk factors for future exacerbations and should be considered as part of comprehensive future risk assessment.

A further limitation is that 18 of the 26 studies identified in this review were from North American populations and we demonstrated that the OR for an exacerbation following an index exacerbation were lower for these studies compared to others, possibly due to differences in healthcare systems in North America and other continents. The results from five different European countries (28) were heterogeneous and this may highlight differences in how asthma exacerbations are managed between countries. The reason for these differences could come from variations in asthma management, including medications, follow-up and asthma action plans, as well as varying compliance with medications, environmental factors and cultural differences (28). There was also evidence of publication bias in the included studies, although these had minimal effect on the overall odds ratio of the meta-analyses performed.

A limitation of the methodology used in this review is that the literature search, data extraction and quality assessment processes were performed by one individual, leading to potential bias. The effects of this were mitigated by detailed discussion and involvement of an experienced paediatric clinician at every stage of the review. A second limitation to our methodology is that our results cannot be generalised to children under five years of age whose results are not included in this review.

The OR and PPV of an index exacerbation being followed by a further exacerbation was higher in the unspecified severity category studies when compared with studies which applied any of the three specified exacerbation severities. This initially seems counterintuitive, as it would be expected that children requiring hospitalisation for asthma, especially requiring PICU admission, would have more severe disease and are therefore more likely to experience a future exacerbation. However, the experience of having symptoms which necessitate a visit to the ED or an admission to hospital may improve treatment compliance and avoidance of triggers for exacerbation and thus reduce the likelihood of further exacerbations.

In summary, an index asthma exacerbation in children aged 5-16 years is a predictor of future acute exacerbation, and this relationship is not necessarily affected by exacerbation severity but is related to the period of follow-up, healthcare system and study methodology.

CONCLUSION

Our review of the literature supports asthma guideline advice that a past exacerbation is predictive of a future exacerbation. Additionally, our study places an estimated magnitude on the OR and PPV for an exacerbation predictive of further relapse and finally our work gives insight into the complexity of the relationship between successive asthma exacerbations in children.

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R.L and S.T contributed to the conception, design, data collection, analysis of the results and to the writing and reviewing of the manuscript. S.T is the guarantor of the paper.

TABLES

Table I – Summary of Key Study Characteristics of Included Studies

Results provided with 95% confidence intervals (CI) in brackets where provided. Studies marked with a * were included in meta-analysis.

Author and Publication Date	Study Design	Study Setting	Data Collection Period	Population/ Inclusion Criteria	Sample Size (n)	Definition of acute exacerbation	Results
Emerman *et al.*, 2001*	Prospective cohort Combining 2 studies with identical protocols	44 EDs in USA and Canada	Studies performed 1997-1998 Follow-up 2 weeks after index ED visit	Children aged 2-17 years with ED visit for acute asthma Mean age – 7.99 years 59% male 19% White, 55% Black, 24% Hispanic, 2% other	1184 recruited, follow-up data available for 762	ED visit with physician diagnosed acute asthma	Factors associated with acute asthma relapse - ED visits for asthma in past year (per 5 visits) → OR 1.2 (1.0, 1.5) - Urgent clinic visits for asthma in past year (per 5 visits) → OR 1.1 (0.9, 1.3)
Lafata *et al.*, 2002	Retrospective cohort study using routinely acquired data	Michigan, USA	1992-1996 2 year observation – 1 baseline year and 1 follow-up year	Children aged 5-14 years, with 1 hospitalisation or 2 outpatient encounters for asthma and ≥1 paediatrician office visit for each year of inclusion Mean age - 8.7 years 63% male 49% White, 44% African American, 7% other	452	ED visit or hospitalisation for asthma	Factors associated with ED use - ED visit for asthma in prior year → OR 8.26 (4.79, 14.25) - Hospital admission for asthma in prior year → OR 0.85 (0.32, 2.22) Factors associated with ED or hospital admission for asthma - Prior ED visit for asthma → OR 7.97 (4.64, 13.71)

Chen *et al*., 2003	Prospective cohort	Children's Hospital, St Louis, USA	Admissions between June-December 1999 1 year follow-up	Children aged 4-18 years, hospitalised for asthma Mean age - 8.22 years 65% male 77% African American, 21% White, 2% other	115	Hospitalisation for asthma	Lifetime history of hospitalisations as a predictor of future hospitalisation → OR 5.36 (1.90, 15.14)
Schatz *et a*l., 2003	Retrospective cohort study using routinely acquired data	California, USA	1998-1999 2 year observation – 1 baseline year and 1 follow-up year	Individuals aged 3-64 years with asthma Children - 62.2% male	11,101 in total, 6904 children aged 3-17 years	Hospitalisation or ED visit for asthma	In children aged 3-17, 1998 hospitalisations as a predictor for asthma hospitalisation in 1999 → OR 3.37 (1.61, 7.04)
McCoy *et al*., 2006	Data from RCT used as an observational study	19 American Lung Association Clinical Research Centres, USA	Recruitment from 15th September - 30th November 2000 Follow-up for 14 days after each injection (28 days total)	Volunteers aged 3-64 years with physician diagnosed asthma Of children originally enrolled - 60% male - 60.5% White, 28.7% Black, 5.6% Hispanic, 4.4% other	2032 enrolled, 1949 completed trial, 353 children aged 3-10 years	New or increased OCS or an unscheduled healthcare encounter for asthma	History of intubation for asthma, hospitalisation ≥2 times for asthma, ≥3 courses of OCS for asthma in past year, or ≥2 unscheduled health contacts for asthma in past year in children aged 3-10 as a predictor of exacerbations → OR 2.19 (1.18, 4.06)
Reznik *et al*., 2006	Retrospective case-control	Children's Hospital, New York, USA	Admissions between January 1998-December 2004 30 day follow-up	Cases - children aged 0-21 years hospitalised for asthma and readmitted within 30 days of discharge for same reason Controls - children aged 0-21 years hospitalised for asthma but not readmitted within 30 days of discharge Mean age – 5.99 years 61% male 62.2% Hispanic, 34.2% African American, 3.6% other	445 Cases – 152 Controls – 293	Hospitalisation for asthma	Predictors of early asthma readmission - ED visit for asthma in past year → OR 3.28 (1.55, 6.94) Multivariate analysis of predictors of early asthma readmission - Hospital admission for asthma in past year → OR 1.89 (1.10, 3.25) - Prior ICU admission for asthma → OR 1.99 (0.93, 4.27)

Covar *et al*., 2008*	Data from PACT RCT used as an observational study	USA	Recruited between October 2002-January 2004 Trial period - 48 weeks	Children aged 6-14 years with documented mild-moderate persistent asthma, screening FEV1 ≥80% predicted and methacholine reactivity 61.4% male 44.9% from an minority ethnic group	285	Systemic corticosteroids or emergency care (ED visit or hospitalisation) for acute asthma	Logistic regression analysis of factors at baseline predictive of exacerbation - History of exacerbation requiring corticosteroid course in past year → OR 2.28 (1.59, 3.26) Multivariable model of factors associated with exacerbations - Prednisone course in year prior to study → OR 2.10 (1.42, 3.09)
Miller *et al*., 2008	Prospective cohort	Michigan, USA	Enrolment over 1 year period Follow-up at 2 weeks and 6 months post-ED visit	Children aged 2-17 years presenting to ED for acute asthma Mean age - 8.1 years 61.5% male 71.7% White, 50% Black, 26% Hispanic, 7% American Indian or Alaska native, 2% Asian, 2% other	197 enrolled, follow-up data available for 166	Signs/symptoms compatible with asthma exacerbation (shortness of breath, coughing, wheezing, chest tightness) in a diagnosed asthmatic	Previous severe disease (e.g. systemic corticosteroids, ED visit or hospitalisation for asthma) as a predictor of 6 month morbidity (urgent care, ED or hospital admissions for asthma) → Pearson correlation coefficient 0.17
To *et al*., 2008	Prospective cohort	Children's Hospital, Toronto, Canada	ED visit between January 2003-June 2004 Follow-up at 1 and 6 months post-ED visit	Children aged 2-17 years visiting ED for acute asthma 70% <7 years old 59% male	269 enrolled, 247 completed 1 month follow-up, 220 completed 6 month follow-up	Sudden worsening of symptoms resulting in difficulty breathing often requiring extra medicine to relieve	Predictors of acute asthma episode at 6 month follow-up - Acute asthma episode 6 months prior to baseline → OR 4.73 (2.25, 9.97) Predictors of ED visit at 6 month follow-up - ED visits in 12 months prior to baseline → OR 6.27 (1.54, 7.12)

						symptoms, with/without unscheduled ED/doctor visit	
Haselkorn *et al.*, 2009	Prospective cohort Data from TENOR study	USA	TENOR conducted from 2001-2004 Follow-up with semi-annual visits for 3 years	Children with severe asthma or mild/moderate asthma considered difficult to treat Had ≥2 OCS bursts in past year, ≥2 unscheduled clinic or hospital visits for asthma in past year, requirement for chronic, daily high doses of ICS or ≥5mg oral prednisone or current use of ≥3 medications to control asthma 69% male 62% White, 38% other	4756 637 children aged 6-11 years Data available for 563 children	Use of a corticosteroid burst	Multivariate model including 6 and 12 month events - Recent exacerbation as a predictor of future exacerbation → OR 1.99 (1.51, 2.61) Multivariate model including only 6 month events - Recent exacerbation as a predictor of future exacerbation → OR 3.08 (2.21, 4.28)
Tolomeo *et al.*, 2009	Retrospective cohort study using routinely acquired data	Children's Hospital, New England, USA	Hospitalisation between January-December 2006 Data for 1 year before and after hospitalisation	Children aged 2-15 years admitted to hospital for asthma Mean age - 6.35 years 66% male 36% White, 35% Black, 24% Hispanic, 5% other	298	Hospital admission with primary diagnosis of asthma	Previous asthma-related ED visit as a predictor of: - Subsequent ED visit → OR 3.3 (1.39, 7.96) - Subsequent hospitalisation for asthma → OR 3.1 (1.17, 8.33)
Triasih *et al.*, 2011*	Retrospective cohort	Children's Hospital, Melbourne, Australia	ICU admission between January 1990-December 2004 Mean follow-up 10.3 years	Children aged 2-18 years with asthma admitted to ICU Median age at admission – 7.0 years 59% male	410	ICU admission for asthma	Risk factors for readmission to hospital - Previous hospital admission → OR 3.3 (2.1, 5.3) - Admission in year prior to index admission → AOR 4.5 (2.5, 8.4) - Multiple previous hospital admissions → OR 2.4 (1.3, 4.2) Risk factors for readmission to ICU - Previous hospital admission → OR 16.9 (4.1, 70.4)

							- Admission in year prior to index admission → AOR 4.7 (2.4, 9.3) - Multiple previous hospital admissions → OR 3.2 (1.6, 6.7) - Previous ICU admission → AOR 2.4 (0.8, 6.7)
Wu *et al*., 2011*	Data from CAMP RCT used as an observational study	USA	Enrolment between December 1993-September 1995 Follow-up over 4 years	Children aged 5-12 years with mild/moderate persistent asthma 60% male 68% White, 14% Black, 9% Hispanic, 9% other	1041 enrolled 1019 completed daily diary cards	Episode requiring ≥3 days use of OCS, hospitalisation, or ED visit due to asthma (ATS/ERS statement)	History of ED visits or hospitalisations in prior year as a predictor of having ≥1 severe exacerbations → regression coefficient 0.73 (0.50, 0.96) History of ≥3 days of treatment with OCS in prior 3 months as a predictor of having ≥1 severe exacerbations → regression coefficient 0.40 (0.17, 0.62)
Li *et al*., 2012	Retrospective cohort study using routinely acquired data	Ontario, Canada	ED visit between 14th April 2006-28th February 2009 Follow-up for 1 year	Children aged 2-17 years with prevalent asthma with unplanned visit to ED for asthma 38.4% aged 2-5 years 63.1% male	29391	ED visit for asthma	Adjusted hazard ratios for ED re-visits - Asthma admission(s) in prior 2 years → HR 1.45 (1.35, 1.55) - Asthma ED visit(s) in prior 2 years → HR 2.03 (1.91, 2.14) Adjusted hazard ratios for hospital admissions - Asthma admission(s) in prior 2 years → HR 2.87 (2.43, 3.39) - Asthma ED visit(s) in prior 2 years → HR 1.85 (1.57, 2.19)
van den Bosh *et al*., 2012*	Retrospective case-control	4 hospitals in Netherlands	January 1994-October 2006	Cases - children with doctor diagnosed asthma admitted to PICU for acute asthma Controls - patients with asthma who never needed PICU	230 Cases – 66 Controls – 164	PICU admission for acute asthma	Earlier hospitalisation for asthma (non-PICU) as a risk factor for PICU admission → OR 5.4 (1.34-21.45)

				admission for any reason Median age at PICU admission - 5.2 years 77% White			
Visitsunthorn *et al*., 2013	Retrospective case-control	Children's Hospital, Bangkok, Thailand	January 2006-December 2007 1 year follow-up	Children aged ≤14 years admitted to hospital for acute asthma 50% >6 years old 64.5% male	76 1 admission – 56 Readmission – 20	Acute asthma that was severe or did not improve after 3 doses of bronchodilator nebulisation	ICU admission at first admission as a risk factor for readmission → OR 29.62 (3.35, 262.18)
Kenyon *et al*., 2014	Retrospective cohort study using routinely acquired data	USA	Discharges between 1st July 2008–30th June 2010 1 year follow-up	Children ≥2 years discharged from hospital after admission for asthma 61% aged 5-18 years 61.1% male 46.6% Black, 27.3% White, 16.8% Hispanic, 7.9% other	36601 Contributing 44203 hospitalisations	Hospital admission for asthma	Prior year admission as a risk factor for asthma rehospitalisation - 7 days → OR 2.0 (1.4, 2.7) - 15 days → OR 2.7 (2.1, 3.3) - 30 days → OR 2.9 (2.5, 3.4) - 60 days → OR 3.5 (3.1, 3.9) - 180 days → OR 3.5 (3.3, 3.8) - 365 days → OR 3.6 (3.4, 3.8)
Zeiger *et al*., 2015	Retrospective cohort study using routinely acquired data	California, USA	2010-2011 1 baseline year and 1 outcome year	Children aged 5-11 years who met HEDIS criteria for persistent asthma Blood eosinophil level determined in 2010 With eosinophil level: - Mean age - 7.7 years - 61.9% male - 45.3% Hispanic, 24.6% White, 17.4% Black	2451 With eosinophil count – 333	Asthma outpatient visits requiring systemic corticosteroids within ± 7 days or asthma ED visits or hospitalisation	History of exacerbation as a risk factor for exacerbation - Adjusted rate ratio 2.35 (1.61, 3.44) - Adjusted risk ratio 1.94 (1.37, 2.73)

Engelkes *et al.*, 2016*	Retrospective cohort study using routinely acquired data	Netherlands	1st January 2000-1st January 2012 Mean follow-up 2.46 years	Children with asthma aged 5-18 years Mean age - 10.5 years 58.7% male	14,303	Hospitalisation, ED visit, or prescription of systemic corticosteroids for ≥3 days for asthma	Prior exacerbations as a risk factor for exacerbation - Total cohort → model 1 (relative rate – 1.99 (1.40, 2.83)), model 2 (relative rate – 2.17 (1.30, 3.60)) - Children with ≥1 exacerbation ever → model 1 (relative rate – 1.60 (1.37, 1.88)), model 2 (relative rate – 1.52 (1.19, 1.94)) Exacerbations as a risk factor for non-frequent exacerbations compared to frequent exacerbations - <2 vs ≥2 → OR 2.11 (1.66, 2.68) vs OR 1.93 (1.42, 2.63) - <3 vs ≥3 → OR 2.43 (1.84, 3.23) vs OR 1.99 (1.35, 2.94)
Quezada *et al.*, 2016*	Data from SARCA and SARA RCTs used for an observational study	USA	2007-2011 24 week treatment period	SARCA trial – children aged 6-17 years, with poor asthma control, being treated with inhaled glucocorticoids 62% male 39% White, 49% Black, 12% other	718 enrolled Data for 295 from SARCA	Requirement for OCS or urgent health care visit for asthma symptoms	83% of children with an exacerbation had an unscheduled visit for asthma in the previous year and 80% had been treated with OCS 69% of children without an exacerbation had an unscheduled visit for asthma in the previous year and 61% had been treated with OCS
Costa *et al.*, 2018*	Retrospective case-control	Goiania, Brazil	June 2012-August 2013 Data collected for 1 year prior to ED visit	Cases - children aged 4-14 years, admitted to ED for asthma who had ≥3 previous episodes of bronchospasm Controls - asthmatic children without exacerbation recruited during outpatient appointment Cases	153 Cases – 92 Controls – 61	Increased symptoms requiring change in medication, judged by physician according to	≥3 ED visits in past year for asthma as a risk factor for asthma exacerbation → incidence risk ratio 1.40 (1.01, 1.95)

				- Median age - 7 years - 56% male - 62% White Controls - Median age - 8 years - 42% male - 28% White		ATS/ERS statement. Severe exacerbation – hospital admission or course of OCS for asthma	
Grunwell *et al*., 2018	Retrospective case-control Data from outpatient asthma clinical research studies at Emory University	Georgia, USA	January 2004-December 2015	Cases - children aged 6-18 years with historical admission to PICU for acute asthma Controls – asthmatic children without prior PICU admission Cases - Median age - 10 years - 56.7% male - 52.3% Black, 35.2% White, 12.5% other Controls - Median age - 12 years - 61.8% male - 71.8% Black, 17.1% White, 11.2% other	579 Cases – 170 Controls – 409	PICU admission, hospitalisation or ED visit for asthma	Hospitalisation for asthma in year prior to data collection was associated with increased odds of PICU admission → OR 8.19 (4.83, 13.89)
To *et al*., 2018	Retrospective cohort study using routinely acquired data	Toronto, Canada	April 2008-March 2014 1 year follow-up	Individuals aged 5-99 years with ED visit for asthma Aged 5-19 years - Mean age - 12.15 years - 57% male - 31% in most marginalised ethnic concentration quintile	58,366 18,352 aged 5-19 years	ED visit for asthma	Adjusted relative risk of asthma ED return visit within 1 year of ED discharge in children aged 5-19 → 1.13 (1.03, 1.25)

Turner *et al*., 2018*	Retrospective cohort study using routinely acquired data	UK	January 1999-December 2012 1 baseline year and 1 outcome year	Children aged 5-12 years diagnosed with asthma Mean age – 9 years 57% male	3776	Hospitalisation, ED admission or OCS for asthma (ATS/ERS)	Previous asthma attack as a risk factor for ≥1 attack - 1 → OR 3.74 (2.92, 4.80) - 2+ → OR 7.72 (5.55, 10.74)
Alsheri *et al*., 2020*	Retrospective case-control	Abha Hospital, Saudi Arabia	January 2014-December 2018	Cases - children aged 2-14 years admitted to PICU for acute asthma Controls – children admitted to the ward for acute asthma Cases - Mean age - 6.3 years - 41.7% male Controls - Mean age - 4.6 years - 42.7% male	320 Cases – 72 Controls – 248	PICU or hospital admission for asthma	Previous admission to PICU as a risk factor for PICU admission → OR 7.83 (2.58, 23.76)
Engelkes *et al*., 2020*	Retrospective cohort study using routinely acquired data from Netherlands, Italy, UK, Denmark and Spain	Netherlands	January 2008-December 2013	Patients aged 5-17 years with asthma Sub-cohort with severe asthma (requiring high dose ICS + second controller and/or systematic corticosteroids for ≥120 consecutive days) Mean age - 10.4 years (7.2-14.8 years across databases) Male preponderance across all databases	212,060 Severe asthma – 14,283	Use of systemic corticosteroids, ED visit and/or hospitilisation, for worsening asthma	Relative rates of exacerbation in those with history of exacerbation - CPRD – 5.76 (5.25, 6.33) - SIDIAP – 2.53 (2.27, 2.81) - IPCI – 20.04 (12.91, 31.10) - AUH – 45.71 (31.2, 66.92) - PEDIANET – 29.36 (16.25, 53.05) - HSD – 10.07 (4.56, 22.20)

Abbreviations used: AOR – adjusted odds ratio, ATS/ERS – American Thoracic Society/ European Respiratory Society, AUH – Aarhus University Prescription Database, CAMP – Childhood Asthma Management Program, CPRD – Clinical Practice Research Datalink, ED – Emergency

Department, FEV1 – forced expiratory volume in 1 second, HEDIS – Healthcare Effectiveness Data and Information Set, HR – hazard ratio, HSD – Health Search Database, ICS – inhaled corticosteroids, IPCI – Integrated Primary Care Information, mg – milligram, OCS – oral corticosteroids, OR – odds ratio, PACT – Pediatric Asthma Controller Trial, PICU – Paediatric Intensive Care Unit, RCT – randomised controlled trial, SARA – Study of Acid Reflux in Adults with Asthma, SARCA – Study of Acid Reflux in Children with Asthma, SIDIAP – Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària, TENOR – The Epidemiology and Natural History of Asthma, UK – United Kingdom, USA – United States of America.

Table II – Summary of Quality Assessment Using the EPHPP Quality Assessment Tool for Quantitative Studies

The domains blinding, intervention integrity and analyses were not applicable for any of the studies and were therefore removed.

Retrospective case-control studies were given a not applicable score in the withdrawals and drop-outs domain in accordance with the tool recommendations. Key: 1 – strong, 2 – moderate, 3 – weak, n/a – not applicable.

	Emerman *et al.*, 2001	Lafata *et al.*, 2002	Chen *et al.*, 2003	Schatz *et al.*, 2003	McCoy *et al.*, 2006	Reznik *et al.*, 2006	Covar *et al.*, 2008	Miller *et al.*, 2008	To *et al.*, 2008	Haselkorn *et al.*, 2009	Tolomeo *et al.*, 2009	Triasih *et al.*, 2011	Wu *et al.*, 2011	Li *et al.*, 2012	van den Bosch *et al.*, 2012	Visitsunthorn *et al.*, 2013	Kenyon *et al.*, 2014	Zeiger *et al.*, 2015	Engelkes *et al.*, 2016	Quezada *et al.*, 2016	Costa *et al.*, 2018	Grunwell *et al.*, 2018	To *et al.*, 2018	Turner *et al.*, 2018	Alsheri *et al.*, 2020	Engelkes *et al.*, 2020
Selection Bias	2	1	3	1	2	1	2	2	2	2	1	2	2	1	1	1	1	1	1	2	2	1	1	1	2	1
Study Design	2	2	2	2	1	2	1	2	2	2	2	2	1	2	2	2	2	2	2	1	2	2	2	2	2	2
Confounders	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	1	1	1
Data Collection Methods	2	1	1	1	2	1	1	2	2	2	1	1	1	1	2	2	1	1	1	1	2	2	1	1	2	1
Withdrawals and Drop-Outs	2	1	1	1	2	n/a	2	2	2	3	1	1	2	1	n/a	n/a	1	1	1	2	n/a	n/a	1	1	n/a	1
Global Rating	1	1	2	1	1	1	1	1	1	2	1	1	1	1	1	1	1	1	1	2	1	1	1	1	1	1

Table III – Key Results Shown by Index and Subsequent Exacerbation Type

		Category of Subsequent Exacerbation		
		ED	Hospital	PICU
Category of Index Exacerbation	ED	5 studies • ORs – 3.3 (25), 6.27 (24), 8.26 (19) • HR – 2.03 (32) • RR – 1.13 (34)	3 studies • ORs – 3.1 (25), 3.28 (22) • HR 1.85 (32)	No studies
	Hospital	2 studies • OR – 0.85 (19) • HR 1.45 (32)	6 studies • ORs – 1.89 (22), 3.3 (35), 3.37 (23), 3.6 (31), 5.36 (16) • HR – 2.87 (32)	3 studies • ORs – 5.4 (37), 8.19 (30), 16.9 (35)
	PICU	No studies	2 studies • ORs – 2.18 (22), 29.62 (38)	2 studies • ORs – 2.4 (35), 7.83 (26)

Abbreviations used: ED – Emergency Department, HR – hazard ratio, OR – odds ratio, PICU – Paediatric Intensive Care Unit, RR – relative risk.

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FIGURE LEGENDS

Figure 1 – PRISMA Flow Diagram

Details of the search and study inclusion process, including reasons for exclusion of full-text articles reviewed.

Figure 2 – Exacerbation Outcomes

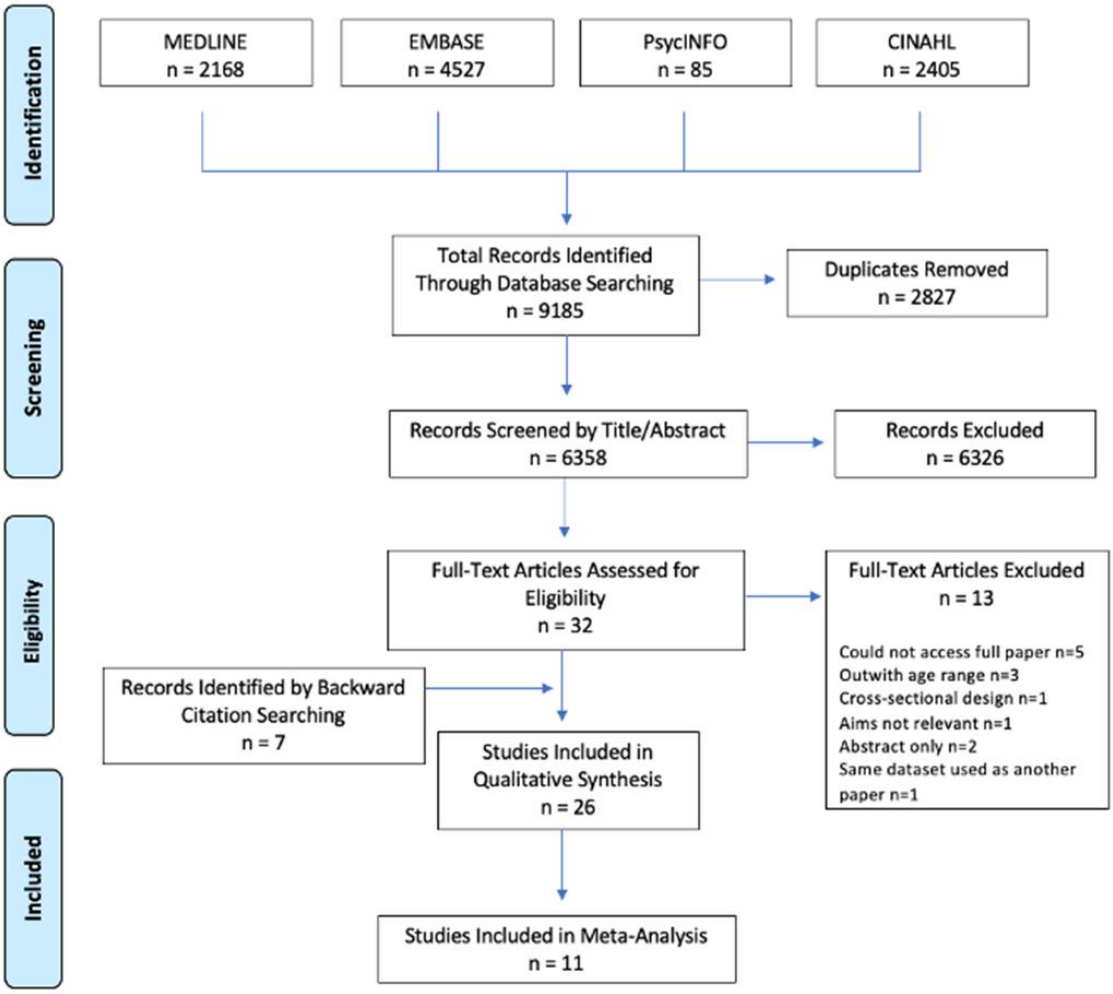
Shows the number of studies which relate different categories of exacerbations at baseline to risk of future exacerbations.

Figure 3 – Forest Plot of Studies Assessing Past Exacerbation (Unspecified Severity) Predicting Future Exacerbation

Data presented separately for five of the databases used in Engelkes *et al*., 2020.

Figure 4 – Forest Plots Based on Exacerbation Severity Definition and Location of Study Publication (A-D)

In Panel D data are presented separately for five of the databases used in Engelkes *et al*., 2020.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Screening
Eligibility
Included
MEDLINE
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EMBASE
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PsycINFO
n = 85
CINAHL
n = 2405
Total Records Identified Through Database Searching
n = 9185
Duplicates Removed
n = 2827
Records Screened by Title/Abstract
n = 6358
Records Excluded
n = 6326
Full-Text Articles Assessed for Eligibility
n = 32
Full-Text Articles Excluded
n = 13
Could not access full paper n=5
Outwith age range n=3
Cross-sectional design n=1
Aims not relevant n=1
Abstract only n=2
Same dataset used as another paper n=1
Records Identified by Backward Citation Searching
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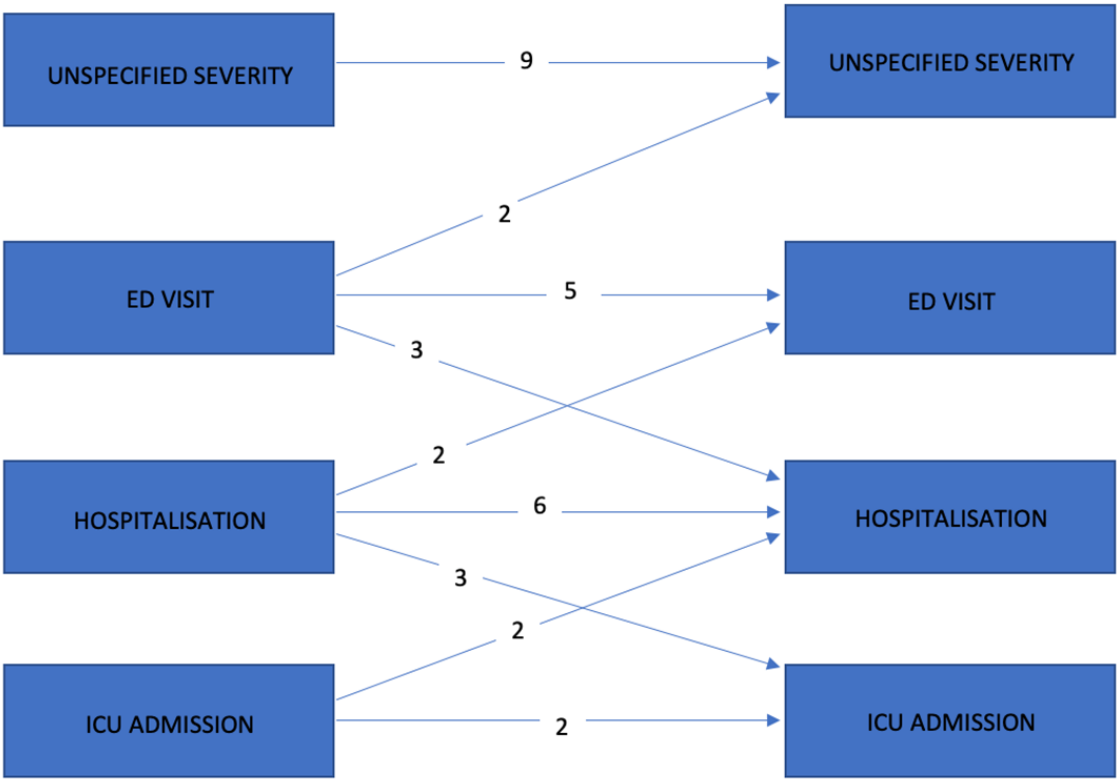
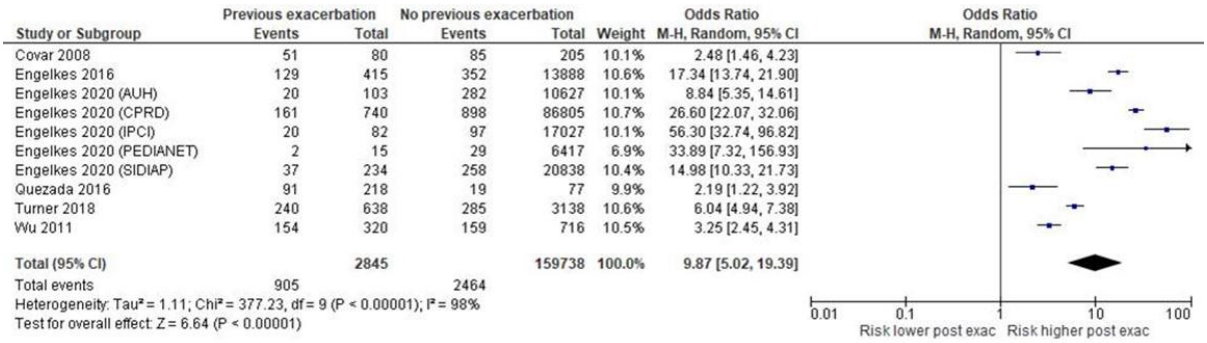
Studies Included in Qualitative Synthesis
n = 26
Studies Included in Meta-Analysis
n = 11

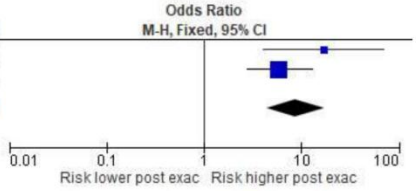

UNSPECIFIED SEVERITY
9
UNSPECIFIED SEVERITY
2
ED VISIT
5
ED VISIT
3
2
HOSPITALISATION
6
HOSPITALISATION
3
2
ICU ADMISSION
2
ICU ADMISSION


Previous exacerbation
No previous exacerbation
Odds Ratio
Odds Ratio
Study or Subgroup
Events
Total
Events
Total
Weight
M-H, Random, 95% CI
M-H, Random, 95% CI
Covar 2008 51 80 85 205 10.1% 2.48 [1.46, 4.23]
Engelkes 2016 129 415 352 13888 10.6% 17.34 [13.74, 21.90]
Engelkes 2020 (AUH) 20 103 282 10627 10.1% 8.84 [5.35, 14.61]
Engelkes 2020 (CPRD) 161 740 898 86805 10.7% 26.60 [22.07, 32.06]
Engelkes 2020 (IPCI) 20 82 97 17027 10.1% 56.30 [32.74, 96.82]
Engelkes 2020 (PEDIANET) 2 15 29 6417 6.9% 33.89 [7.32, 156.93]
Engelkes 2020 (SIDIAP) 37 234 258 20838 10.4% 14.98 [10.33, 21.73]
Quezada 2016 91 218 19 77 9.9% 2.19 [1.22, 3.92]
Turner 2018 240 638 285 3138 10.6% 6.04 [4.94, 7.38]
Wu 2011 154 320 159 716 10.5% 3.25 [2.45, 4.31]
Total (95% CI) 2845 159738 100.0% 9.87 [5.02, 19.39]
Total events 905 2464
Heterogeneity: Tau² = 1.11; Chi² = 377.23, df = 9 (P < 0.00001); I² = 98%
Test for overall effect: Z = 6.64 (P < 0.00001)
0.01
0.1
1
10
100
Risk lower post exac
Risk higher post exac

A. Studies Assessing Past Hospitalisation Predicting Future PICU Admission

Study or Subgroup	Previous exacerbation Events	Total	No previous exacerbation Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Triasih 2011	66	292	2	118	25.0%	16.94 [4.08, 70.39]
van den Bosch 2012	56	140	9	89	75.0%	5.93 [2.75, 12.77]
Total (95% CI)		**432**		**207**	**100.0%**	**8.68 [4.42, 17.07]**
Total events	122		11			

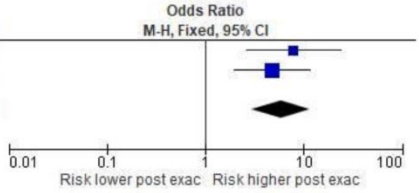
Heterogeneity: Chi² = 1.80, df = 1 (P = 0.18); I² = 44%
Test for overall effect: Z = 6.27 (P < 0.00001)



B. Studies Assessing Past PICU Admission Predicting Future PICU Admission

Study or Subgroup	Previous exacerbation Events	Total	No previous exacerbation Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Alsheri 2020	10	15	62	305	36.3%	7.84 [2.59, 23.77]
Triasih 2011	10	22	58	388	63.7%	4.74 [1.96, 11.48]
Total (95% CI)		**37**		**693**	**100.0%**	**5.87 [2.96, 11.64]**
Total events	20		120			

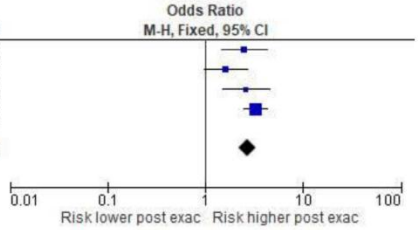
Heterogeneity: Chi² = 0.48, df = 1 (P = 0.49); I² = 0%
Test for overall effect: Z = 5.06 (P < 0.00001)



C. Studies with Available Data Published from North America

Study or Subgroup	Previous exacerbation Events	Total	No previous exacerbation Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Covar 2008	51	80	85	205	16.1%	2.48 [1.46, 4.23]
Emerman 2001	26	183	54	579	20.8%	1.61 [0.98, 2.66]
Quezada 2016	88	200	22	95	15.6%	2.61 [1.50, 4.53]
Wu 2011	154	320	159	716	47.5%	3.25 [2.45, 4.31]
Total (95% CI)		**783**		**1595**	**100.0%**	**2.69 [2.19, 3.30]**
Total events	319		320			

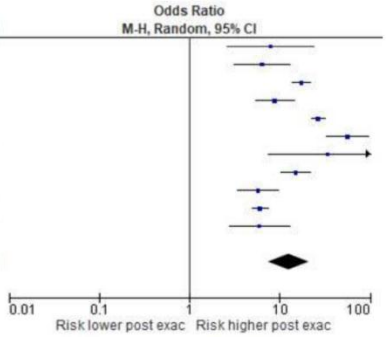
Heterogeneity: Chi² = 5.87, df = 3 (P = 0.12); I² = 49%
Test for overall effect: Z = 9.44 (P < 0.00001)



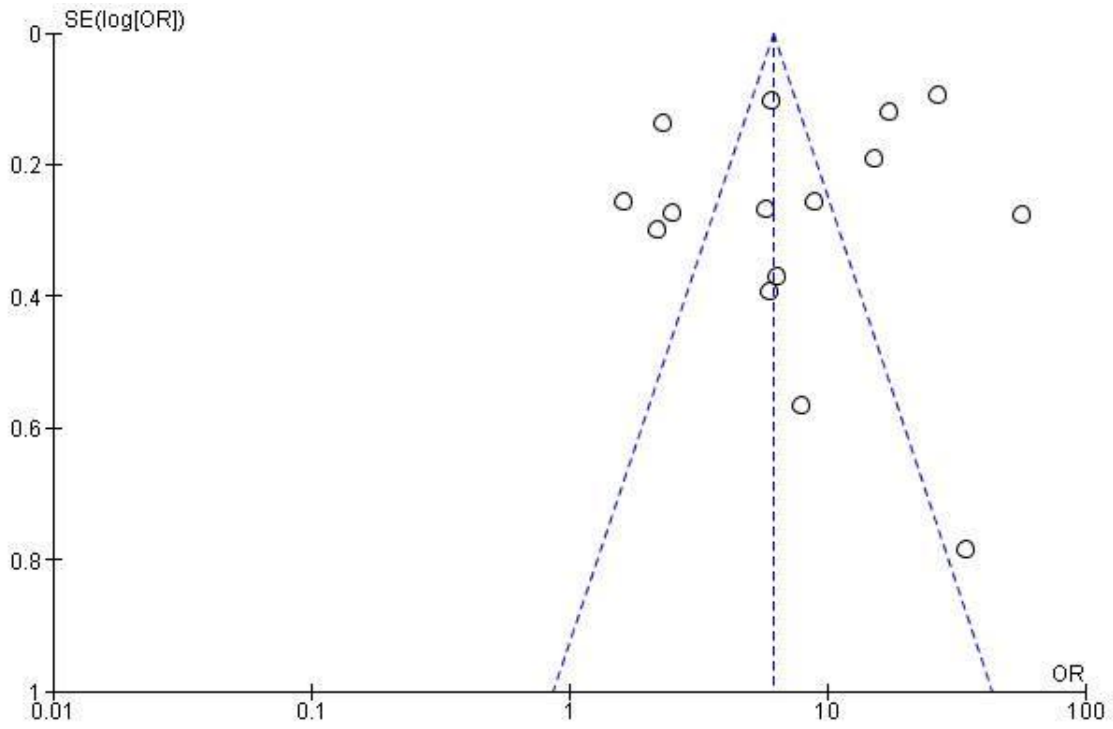
D. Studies with Available Data Published Outside of North America

Study or Subgroup	Previous exacerbation Events	Total	No previous exacerbation Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Alsheri 2020	10	15	62	305	7.2%	7.84 [2.59, 23.77]
Costa 2018	73	96	19	57	8.8%	6.35 [3.08, 13.08]
Engelkes 2016	129	415	352	13888	10.4%	17.34 [13.74, 21.90]
Engelkes 2020 (AUH)	20	103	282	10627	9.6%	8.84 [5.35, 14.61]
Engelkes 2020 (CPRD)	161	740	898	86805	10.4%	26.60 [22.07, 32.06]
Engelkes 2020 (IPCI)	20	82	97	17027	9.5%	56.30 [32.74, 96.82]
Engelkes 2020 (PEDIANET)	2	15	29	6417	5.5%	33.89 [7.32, 156.93]
Engelkes 2020 (SIDIAP)	37	234	258	20838	10.0%	14.98 [10.33, 21.73]
Triasih 2011	143	164	133	246	9.6%	5.79 [3.43, 9.75]
Turner 2018	240	638	285	3138	10.4%	6.04 [4.94, 7.38]
van den Bosch 2012	56	140	9	89	8.6%	5.93 [2.75, 12.77]
Total (95% CI)		**2642**		**159437**	**100.0%**	**12.36 [7.33, 20.84]**
Total events	891		2424			

Heterogeneity: Tau² = 0.67; Chi² = 203.76, df = 10 (P < 0.00001); I² = 95%
Test for overall effect: Z = 9.44 (P < 0.00001)



SUPPLEMENT



Supplemental Figure 1 – Funnel Plot Incorporating 16 Populations from the 11 Studies Included in the Meta-Analysis

Studies included - Alsheri *et al.,* 2020; Costa *et al.,* 2018; Covar *et al.,* 2008; Emerman *et al.,* 2001; Engelkes *et al.,* 2016; Engelkes *et al.,* 2020; Quezada *et al.,* 2016; Triasih *et al.,* 2011; Turner *et al.,* 2018; van den Bosch *et al.,* 2012; Wu *et al.,* 2011.

.

Study Design	Author	Outcome	Positive Predictive Value
Randomised Controlled Trial	Covar *et al.*, 2008	≥1 prednisone course in prior year + exacerbation during follow-up	0.43
	Wu *et al.*, 2011	ED visit or hospitalisation in year prior to randomisation + exacerbation during follow-up	0.58
	Quezada *et al.*, 2016	Unscheduled visit in prior year + future exacerbation	0.77
Prospective Cohort Study	Emerman *et al.*, 2001	Hospitalisation in prior year + future exacerbation	0.31
	Chen *et al.*, 2003	Hospitalisation + readmission in following year	0.30
	Miller *et al.*, 2008	ED visit + urgent care visit in following 6 months	0.14
	To *et al.*, 2008	ED visit + exacerbation in following 6 months	0.54
Routinely Acquired Data	Tolomeo *et al.*, 2009	Hospitalisation + ED visit in following year	0.28
	Kenyon *et al.*, 2014	Hospitalisation + readmission in following year	0.17
	Engelkes *et al.*, 2016	Exacerbation in year prior to cohort entry + exacerbation during follow-up	0.28
	To *et al.*, 2018	ED visit + ED visit in following year	0.12
	Turner *et al.*, 2018	Exacerbation in baseline year + exacerbation in outcome year	0.43
	Engelkes *et al.*, 2020	Exacerbation + future ED visit/hospitalisation CPRD SIDIAP IPCI AUH PEDIANET	 0.15 0.13 0.19 0.08 0.06
Retrospective Case-Control	van den Bosch *et al.*, 2012	Hospitalisation + future PICU admission	0.73
	Visitsunthorn *et al.*, 2013	Hospitalisation + readmission	0.26
	Costa *et al.*, 2018	≥3 ED visits in prior year + exacerbation at baseline	0.78
	Alsheri *et al.*, 2020	PICU admission + future PICU admission	0.25

Supplemental Table I – Positive Predictive Values for Studies Stratified by Methodology

Abbreviations used: AUH – Aarhus University Prescription Database, CPRD – Clinical Practice Research Datalink, ED – Emergency Department, IPCI – Integrated Primary Care Information, PICU – Paediatric Intensive Care Unit, SIDIAP - Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària.

Search Strategy

Ovid MEDLINE(R) – 1946 to December Week 5 2020

1. exp Asthma/
2. asthma$.tw.
3. (asthma$ adj3 attack$).tw.
4. (asthma$ adj3 exacerbation$).tw.
5. (p?ediatric adj3 asthma$).tw.
6. (acute adj3 asthma$).tw.
7. 1 or 2 or 3 or 4 or 5 or 6
8. exp Child/
9. p?ediatric$.tw.
10. 8 or 9
11. (risk adj3 factor$).tw.
12. 7 and 10 and 11

Limits → English language, Human studies, no Review articles, publication year 2000-current

Ovid EMBASE classic + EMBASE – 1947 to 2021 January 08

1. exp Asthma/
2. asthma$.tw.
3. (asthma$ adj3 attack$).tw.
4. (asthma$ adj3 exacerbation$).tw.
5. (p?ediatric adj3 asthma$).tw.
6. (acute adj3 asthma$).tw.
7. 1 or 2 or 3 or 4 or 5 or 6
8. exp Child/
9. p?ediatric$.tw.
10. 8 or 9
11. (risk adj3 factor$).tw.
12. 7 and 10 and 11

Limits → English language, Human studies, no Review articles, publication year 2000-current

APA PsycInfo 1806 to January Week 1 2021

1. exp Asthma/
2. asthma$.tw.
3. (asthma$ adj3 attack$).tw.
4. (asthma$ adj3 exacerbation$).tw.
5. (p?ediatric adj3 asthma$).tw.
6. (acute adj3 asthma$).tw.
7. 1 or 2 or 3 or 4 or 5 or 6

8. child$.tw.
9. p?ediatric$.tw.
10. 8 or 9
11. (risk adj3 factor$).tw.
12. 7 and 10 and 11

Limits → English language, Human studies, no Review articles, publication year 2000-current

EBSCO CINAHL

S1. (MH "Asthma+")
S2. TX asthma*
S3. TX asthma* attack*
S4. TX asthma* exacerbation*
S5. TX p?ediatric asthma*
S6. TX acute asthma*
S7. (MH "Child+")
S8. TX p?ediatric*
S9. TX risk factor*
S10. S1 or S2 or S3 or S4 or S5 or S6
S11. (S1 or S2 or S3 or S4 or S5 or S6) AND (S7 or S8)
S12. ((S1 or S2 or S3 or S4 or S5 or S6) AND (S7 or S8)) AND (S9)
S13. (((S1 or S2 or S3 or S4 or S5 or S6) AND (S7 or S8)) AND (S9)) NOT PT review article

Limits → English language, publication year 2000-2021

Rules applied during scoring

Under the selection bias domain, studies were awarded a rating based on how likely the selected population is to be representative of the target population, and, where applicable, the percentage of selected individuals that agreed to participate.

Under the study design domain, studies were awarded a strong rating if they used data from a randomised controlled trial and a moderate rating if they were a case-control or cohort study.

Under the confounders domain, studies were awarded a strong rating if either there were no important differences between groups, or if they controlled for confounders in their analysis, such as through the use of multivariate models.

Under the data collection methods domain, studies were awarded a strong rating if a database of routinely acquired data was used, or if extra measures were taken to ensure the reliability of the data collected. Studies were awarded a moderate rating if methods such as medical record review or parental interviews were used.

Under the withdrawals and drop-outs domain, studies were awarded a rating based on whether drop-outs were reported in terms of numbers and reasons and also the percentage of individuals completing the study. Retrospective case-control studies were awarded a not applicable status for this domain in accordance with the EPHPP tool guidance.

The global rating was determined based on the number of weak ratings each study had received, with a strong global rating being awarded to studies with no weak domains, a moderate global rating for studies with one weak domain and a weak rating for studies with two or more weak domains.

Results of Quality Assessment

Overall, there was a moderate risk of selection bias across the included studies with 14 awarded a strong rating, 11 awarded a moderate rating and one awarded a weak rating. Chen *et al*., 2003 received a weak rating because, even though the identified individuals were deemed very likely to be representative of the target population, only 44% of selected individuals agreed to participate, increasing the likelihood that these individuals were not representative of the overall target population. Although the majority of studies were awarded a strong rating for selection bias because the individuals selected were likely to be representative of the target population identified in the study, their results may not necessarily be generalisable to the wider asthma population as they often used children admitted to hospital, or seen in the ED, and these children may represent a more severe subset of the childhood asthma population.

The majority of studies received a moderate rating for study design as they were either cohort or case-control studies, with only four receiving a strong rating as they used data from randomised controlled trials.

All but one of the studies received a strong rating in the confounders domain due to there either being no differences between the groups in the study or use of appropriate statistical analysis, with multivariate models used to control for potential confounders. Quezada *et al*., 2016 received a weak rating as there was no effort to control for confounding variables either in the methodology or analysis, reducing the validity of the results.

In the data collection methods domain, 16 received a strong rating and 10 received a moderate rating. The latter rating was due to there being a risk of recall bias in these 10 studies due to use of parental and child interviews, or medical record reviews as their means of data collection. There are differences in the way, and the level of detail, that medical professionals document clinical information based on deemed relevance and importance, and therefore medical records are also not a completely reliable source of data. However, due to the retrospective nature of the majority of these studies, these data collection methods were the only ones available.

Within the withdrawals and drop-out domains, six studies had a retrospective case-control design and therefore received a not applicable rating. Of the remaining 20 studies, 12 received a strong rating and seven received a moderate rating. There was a risk of attrition bias in these seven studies due to not reporting withdrawals and drop-outs in terms of both numbers and reasons. However, for all of these studies, greater than 80% of participants completed the study. Haselkorn *et al*., 2009 received a weak rating due to its use of data from the TENOR study which did not report information regarding drop-outs or the percentage of participants completing the study.