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REVIEW

Measuring Medication Adherence in a Population-Based Asthma Administrative Pharmacy Database: A Systematic Review and Meta-Analysis

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Background: Limited studies have systematically reviewed the literature to identify and compare the various database methods and optimal thresholds for measuring medication adherence specific to adolescents and adults with asthma. In the present study, we aim to identify the methods and optimal thresholds for measuring medication adherence in population-based pharmacy databases.

Methods: We searched PubMed, Embase, International Pharmaceutical Abstracts (IPA), Web of Science, Google Scholar, and grey literature from January 1, 1998, to March 16, 2021. Two independent reviewers screened the studies, extracted the data, and assessed the quality of the studies. A quantitative knowledge synthesis was employed.

Results: Thirty-eight (38) retrospective cohort studies were eligible. This review identified 20 methods for measuring medication adherence in adolescent and adult asthma administrative health records. Two measures namely the medication possession ratio (MPR) and proportion of days covered (PDC) were commonly reported in 87% of the literature included in this study. From the meta-analysis, asthma patients who achieved adherence threshold of "0.75–1.00" [OR: 0.56, 95% CI: 0.41 to 0.77] and ">0.5" [OR: 0.71, 95% CI: 0.54 to 0.94] were less likely to experience asthma exacerbation.

Conclusion: Despite their limitations, the PDC and the MPR still remain the most common measures for assessing adherence in asthma pharmacy claim databases. The evidence synthesis showed that an adherence threshold of at least 0.75 is optimal for classifying adherent and non-adherent asthma patients.

Keywords: medication adherence, adherence measures, asthma, adherence thresholds, meta-analysis, administrative health databases, review

Introduction

Achieving targeted clinical outcomes–asthma control, reduced asthma exacerbation and improved lung function – in asthma patients require a certain degree of medication use. Medication adherence evaluates the degree to which patients use their medications as prescribed by their healthcare providers.[1,2] While adherence to treatment is essential to optimize the benefits of therapy, nonadherence has been associated with poor clinical outcomes, increased healthcare cost and low quality of life.[3–5] Medication adherence in adult asthma patients ranges from 30% to 70%[6–8] and these estimates differ by country, age, sex, and ethnicity.[9]

Several methods have been developed to measure medication adherence and the use of records on prescribed medications to indirectly estimate adherence has gained

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prominence due to increasing availability of electronic health records and administrative data.[10,11] The accurate evaluation of medication adherence in large populations using administrative data is important for assessing medication effectiveness, identifying risk factors associated with suboptimal adherence as well as introducing effective interventions for improving adherence.[12,13] However, the use of administrative and pharmacy claim databases–have several shortcomings including incomplete, or missing data and inability to confirm if patients actually ingested their acquired medication.[14,15] Nonetheless, these adherence measures could reflect real-life setting[15] and improve clinical outcomes if the database captures complete coverage of prescribed medications and refill medication history.[12]

Using administrative data, researchers and clinicians are often faced with a dilemma of choosing an appropriate adherence measure from a wide range of measures and approaches in the literature.[16] In particular, the availability of different adherence measures and their variations commonly used in estimating adherence to asthma medications often worsen the plight of researchers in this area. While some investigators have consistently reported common methods for measuring adherence, a wide variety of threshold classification exist.[11,17,18] Two of the most widely used adherence measures that could be estimated from administrative data are the medication possession ratio (MPR) and proportion of days covered (PDC), which estimates the proportion of the time a patient has medication available.[11] The PDC and MPR adherence rate data can be reported as continuous or converted to a dichotomous measure when a patient attains a certain degree of compliance. To identify patients who are adherent to their medication using these measures, a threshold of '≥0.80′ is conventionally used regardless of the clinical contexts; nonetheless, the threshold may differ across medication therapeutic classes or disease condition.[11,19] There is no ideal threshold for measuring adherence to prescribed medications and the selection of arbitrary cut-off value/threshold is of great concern to researchers since there is lack of pharmacological basis underlying decision to choose cut-off values.[11,20] In addition, several studies have proposed and used disease-specific measures to assess adherence to medications among patients with various conditions including asthma.[19,21] Thus, it remains unclear which adherence measure would be appropriate to assess adherence to asthma medications in patient population already known to have high non-adherence rates.

To our knowledge, limited studies have systematically summed up the evidence around adherence measures to identify an appropriate measure for patients with adolescent and adult asthma. In addition, there is dearth of studies that have identified an optimal adherence threshold for the appropriate adherence measure and their association with clinical outcomes in adolescents and adults with asthma. In view of this, we aim to systematically review evidence in extant literature to identify and compare various methods for measuring medication adherence; optimal thresholds for assessing adherence to medications and their association to targeted clinical outcomes in adolescents and adults with asthma.

Materials and Methods

We followed the recommended checklist, the Preferred Reporting Item of Systematic Reviews and Meta-Analyses (PRISMA)[22] to conduct and report the comprehensive systematic review of the selected studies. The protocol of this review was registered in PROSPERO with registration number CRD42020168922.

Literature Search and Search Strategy

The search strategy was developed by the author (MA-B) in consultation with a Health Science Librarian at the Faculty of Medicine, Memorial University of Newfoundland. We performed a comprehensive search in PubMed, Embase, International Pharmaceutical Abstracts (IPA) and hand search in Google Scholar, Web of Science, grey literature (thesis, unpublished papers), ResearchGate and other research platforms. The authors started the exhaustive search on February 1, 2020, and ended on February 5, 2020, and was subsequently updated up to March 16, 2021. The search included articles published from January 1, 1998, to March 16, 2021. The search criteria comprised "MeSH" terms in PubMed, "Emtree" in Embase, keywords and a combination of "MeSH" terms and Keywords and finally "Emtree" and Keywords. MeSH terms used for the search were ("medication adherence"[Mesh]), and ("Asthma"[Mesh]). Keywords used included (prescription[tiab] OR medication[tiab] OR puffer[tiab] OR "inhaled corticosteroid"[tiab]) AND (adherence[tiab] OR compliance[tiab] OR filling[tiab] OR dispensing[tiab] OR dispensed[tiab] OR filled[tiab]) AND ("Asthma"[Mesh] OR asthma[tiab]). Our search focused on human studies and was limited to studies involving asthma patients aged 12 years and older. Additionally, studies published in English language were included in this review. We manually screened the reference lists of the relevant studies to identify additional articles. Also, content experts were contacted to inquire about other related studies. The final

search strategy in all the research databases is summarized in the Supplementary Material in Table S1.

Study Eligibility and Selection

Two reviewers (MA-B, KOB) independently screened the titles and abstracts yielded by the three bibliographic databases for eligibility at the initial stage. The Rayyan software (a free web and mobile app reference manager)[23] was used to expedite the initial screening of the abstracts and titles. Further, Rayyan was used to remove duplicates and sort inclusions and exclusions of the retrieved abstracts. Any disagreement in the selection of the studies was resolved by consensus or arbitration by an independent researcher. After their relevance was assessed, selected articles were further screened. Studies were eligible for inclusion if they met the following criteria: a) included individuals 12 years and older with physician diagnosis of asthma; Physician diagnosis of asthma was defined as any diagnosis based on ICD codes for asthma in claim/administrative databases as well as prescribed asthma-related medications; b) using population-based administrative claim databases; c) studies reporting claim databases medication adherence measures for asthma; d) studies published from January 1, 1998, to March 2021; e) articles written in English and f) studies published only on humans.

Quality Assessment and Risk of Bias

The reviewers independently assessed the risk of bias and quality assessment of the included studies. We adopted the Joanna Briggs Institute checklist[24] to evaluate the risk of bias of the cohort studies. Using the checklist, we assessed the quality of the individual studies based on 10 domains (see Table S2 in the Supplementary Material). Any disagreement that arose from the assessment of the risk of bias of the studies was resolved by an arbitrator (third reviewer). Further, we determined the confidence in the evidence of studies included in the meta-analysis using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE).[25]

Data Extraction

The reviewers used a standardized spreadsheet based on some generic items and relevant information to independently extract the following data: (a) Study ID or author's name, (b) study population, (c) study design, (d) name of the administrative database, (e) location, (f) outcome assessed/study objectives, (g) medication adherence measures/related measures, (h) definition of the measure, (i) Strength and weaknesses/limitations of the measures, and (j) estimated rate of adherence measured/study results. The data extraction process was simultaneously performed by the reviewers (MA-B and KOB). We resolved the disagreements in the data extraction by mutual agreement.

Evidence Synthesis

A priori, we anticipated significant variations particularly in study design and objectives of studies included in this review. This could introduce heterogeneity and impact on conclusions drawn from our evidence synthesis. To mitigate the impact of heterogeneity on evidence synthesized, two separate approaches – quantitative and narrative – were used to synthesize evidence from retrieved studies. Specifically, we presented outcome data which were practicable to quantitatively combine in a meta-analysis. We used narrative/qualitative synthesis for data with significant heterogeneity and impracticable to combine in a quantitative synthesis. This was done to ensure that, sound and solid conclusions could be made from the evidence gleaned from the various studies included in our systematic review.

Qualitative/Narrative Data Synthesis

We conducted a narrative synthesis of studies meeting the inclusion criteria. Narrative synthesis is an approach to the systematic review and synthesis of findings from multiple sources which primarily uses text to summarize and explain the findings of the synthesis.[26] It is used when statistical meta-analysis is not feasible particularly due to substantial methodological and clinical heterogeneity between studies identified.[26] This study sought to find appropriate adherence measures and further determine the optimal adherence threshold for adults with asthma using administrative data. Thus, this narrative synthesis focused on adherence measures reported in the various claims/administrative databases and study findings were grouped by type, definition/equation, cut-off values or thresholds determination of medication adherence measures.

Quantitative Data Synthesis

The main summary measure for the quantitative synthesis was the odds ratio (OR). Review Manager, version 5.4, and Comprehensive Meta-analysis (CMA) software's were used to analyze data for the quantitative synthesis. We employed the random effects model to synthesize the available evidence due to the suspected between study heterogeneity. The effects estimates were synthesized using the generic inverse variance method to estimate the

contribution of each study (expressed in weights) to the pooled effect. Meta-regression was conducted to investigate the source of the between-study heterogeneity. The authors performed a publication bias check by using the 'Orwin's fail-safe Ns', Egger's regression test and Funnel plot.

Results

Identification of Studies

The database search generated a total of 7268 citations (PubMed = 2456, Embase = 4479, IPA = 321, and additional searches from other sources = 12) [see Figure 1]. Duplicate studies were removed using the Rayyan web app reference manager leaving 2756 records. The titles and abstracts of the 2756 records were screened for relevance. After the screening, we retrieved and downloaded 70 articles for full text review and finally excluded 32 studies based on the study's inclusion and exclusion criteria. The remaining 38 retrospective/prospective cohort studies met the inclusion criteria for this review. The flow diagram in Figure 1 summarizes studies identified and excluded at each stage of the review.

Study Characteristics

The general characteristics of the 38 included articles are presented in Table 1. Most of the studies (n = 33) were retrospective cohort studies with pharmacy claims data.[14,15,18,21,27–55] Three studies employed a retrospective design with prospective assessment[45,53,56] and two other studies conducted by Bidwal et al[19] and Vaidya et al[57] were retrospective in design with cross-sectional assessment of medication adherence without follow-up. All 38 articles were published between 2010 and 2020. More than half of the studies were conducted in North America (USA = 23, Canada = 5)[14,15,19,21,26–30,32–34,38,41,43,45–48,50–52,55–60].The

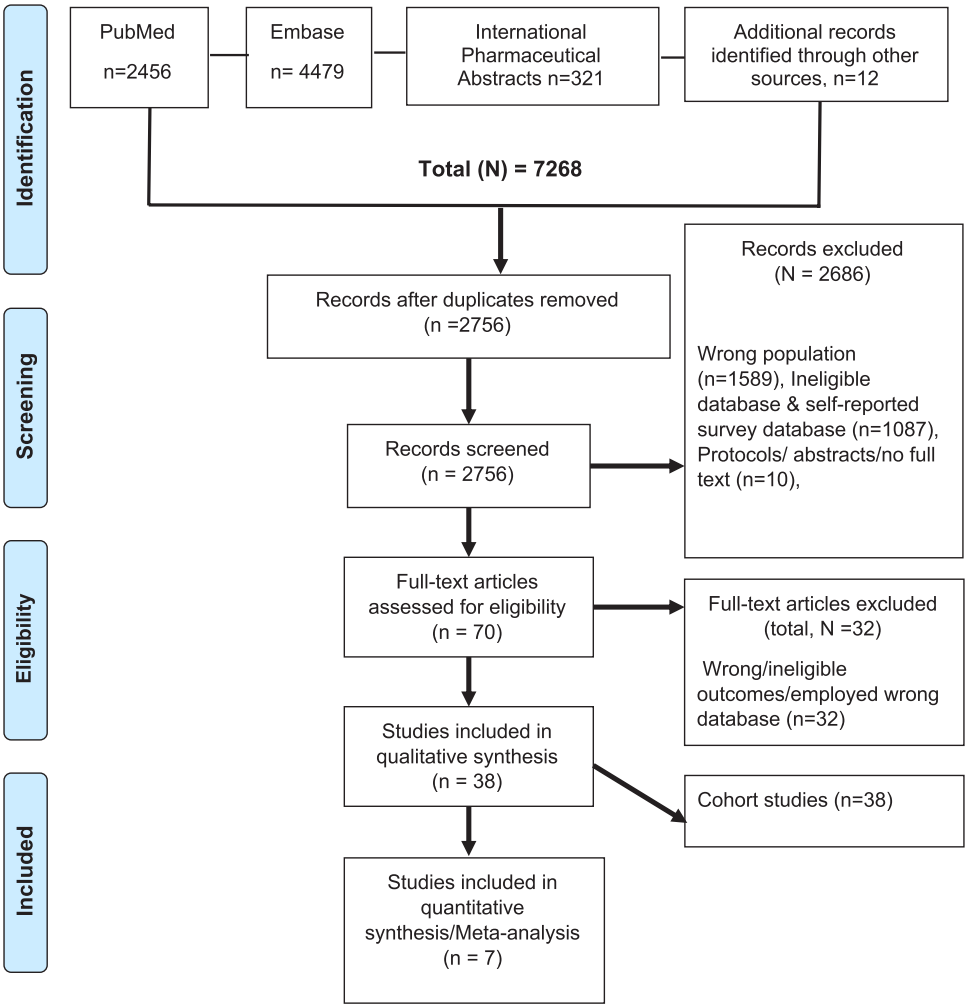

Figure 1 Flow diagram depicting article inclusion and exclusion along with reasons.

Table 1 Summary of Study Findings

Author	Population (Adolescent or Adult Asthma)	Study Type	Name of Administrative Health Database	Location	Outcome Assessed/Study Objectives	Medication Adherence/ Related Measures	Definition of the Measure/Method	Strength and Weaknesses/ Limitations of the Measures	Estimated Rate of Adherence Measured/ Study Results
Averell et al[50]	Patients with diagnosis of asthma 18 years and older initiating ICS/LABA therapy with FF/VI, B/F, or FP/SAL between January 1, 2014 and June 30, 2016. (n=3764+3339 = 7103).	Retrospective cohort study	Medical and Pharmacy claims data, and enrollment information from IQVIA™ Health Plan Claims Data	United States	The primary outcome was medication adherence. Secondary outcome included proportion of patients achieving PDC ≥0.5 and PDC ≥0.8 and persistence with index medication	PDC	PDC calculated based on dispensing data. Defined as the ratio of covered days of asthma medications to days in the measurement period.	1) The use of claim for a filled prescription does not indicate confirmation of usage of the medication. 2) Also, the PDC does not include medication usage during inpatient visits.	The study found significantly higher mean PDC for FF/VI versus B/F (0.453 vs 0.345; adjusted $p < 0.001$) and FP/SAL (0.446 vs 0.341; adjusted $p < 0.001$).
Backer et al[51]	Medical records of 300 patients referred with a suspected asthma during a one-year period. A total of 171 verified asthma cases were identified.	Retrospective register-based study	Danish Registry of Medicinal Product Statistics (Collected one-year data on dispensed medicine).	Respiratory Outpatient Clinic at Bispebjerg Hospital, Copenhagen, Denmark.	Medication adherence/ redemption.	Two measures were used. 1): Defined as a minimum of 2 redeemed prescriptions of controller medications prescribed by the outpatient clinic. 2): PDC	PDC defined as the percentage of days a patient had access to medication based on the amount of medication collected, assuming daily use of medication was prescribed. The defined daily doses (DDDs) for each redemption was used for the calculation.	Drug adherence could have been overestimated since dispensed medications used for PDC calculation does not necessarily indicate actual use of medication.	Using PDC, the study found a higher rate of adherence to ICS in the verified asthma group compared to the unverified asthma group (88% vs 30%, $p = 0.004$).

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Balkrishnan and Christensen[52]	The study included a total of 1595 older adults aged 65 years and older with chronic respiratory diseases including asthma with usage of inhaled corticosteroids for a period of 2 years.	Retrospective study	HMO-claim records/ database (containing prescription refill records)	Seven states in the USA.	Long-term inhaled corticosteroid adherence	Three (3) Medication possession indexes; and a refill regularity measure namely: 1): Med-Total (proposed by Steiner et al) 2): Med-Out 3): Suissa et al measure of regularity of inhaler refills 4) MPR	1): Med-Total = (total number of days of drug supply dispensed)/(365-number of days hospitalized). 2): Med-Out = (Number of days without medication in the year)/(365−days hospitalized). 3): The third index was defined as the monthly cumulative proportion of canisters dispensed during that 12-month period for each subject.	1): The Med-Total may be may not be sensitive to episodic variations in obtaining medications. 2): Studies has documented that Med-Out index is more strongly associated with therapeutic outcomes.	
Bidwal et al[19]	A total of 121 adult persistent asthma patients receiving medication refills were included.	Retrospective study from cross-sectional data.	Electronic chart review was adopted to extract patients' data who obtained asthma medication from Community Health Clinic Ole.	USA	Medication adherence rates: strategies to improve adherence.	1): MPR for asthma controller medications. MPR threshold used were: Medium-high (MPR ≥ 0.5), Low (MPR < 0.5). Full or optimal medication adherence (MPR ≥ 0.8). 2): Asthma medication ratio (AMR). If an AMR ≥0.5, then it means that there is an indication of a therapeutic effect and adequate control in asthma patients.	1): MPR = calculated as the sum of the days' supply for medication fills divided by the time from first supply fill until the end of the measurement period. The Medication day supply = calculated for each medication based on dispensed quantity and prescription directions. The authors used SAS software to compute MPR. 2): AMR = sum of controller medications dispensed divided by the sum of the controller medications and short-acting beta-2 agonists dispensed.	The MPR which is a secondary measure of adherence cannot be use to confirm whether patients actually used their prescribed inhalers with precise technique.	The study found full adherence rate among individuals as 8.3%. Nonadherence rate was 66.1%.

Blais et al[54]	A cohort of 4190 ICS-naive patients with diagnosis of asthma aged 18–45 years were eligible.	Retrospective cohort study.	Two administrative health databases of Quebec (the Regiedel'Assurance Maladie du Quebec (RAMQ)) and the Maintenance et Exploitation des Donnees pour l'Etude de la Clientele Hospitaliere (MED-ECHO)	Canada	To develop a new measure of patients' adherence	Proportion of prescribed days covered (PPDC). PPDC is a modification of PDC.	PPDC defined as the ratio of the total days' supply dispensed to the total days' supply prescribed during the study period.	1): The PPDC could be used to account for the non-adherence attributed to patients when measured with PDC which could be as a result of non-prescribing of ICSs for daily use. The PPDC also account of differing prescribing patterns. In other words, the PPDC adjust for prescribing patterns used in administrative databases. 2): Using PDC to measure adherence has been documented to be very low among patients with asthma (low as 30%).	During a one year study, the mean PPDC and PDC were 52.6% and 18.1%, respectively.
Blais et al[58]	Data for 1108 ICS original prescription stored in the 40 pharmacies and a second sample of 2676 ICS prescriptions from reMed (medication registry) were collected.	Retrospective study.	Québec prescription claims databases for inhaled corticosteroids.	40 community pharmacies in Québec, Canada.	To evaluate the accuracy of the days' supply and number of refills allowed, develop correction factors and used in medication adherence calculation.	Concordance for days' supply, concordance for the refills allowed.		NR	There was a moderate accuracy in terms of the days of supply among those aged 0–11 years, while a substantial accuracy was recorded among those aged within 12–64 years.

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Blais et al[53]	Included both 198 children and 208 adults with one ICS prescription in their medical chart between 2010 and 2012. Focus will be on the 208 adults.	Retrospective and prospective study.	Registre de données en Santé Pulmonaire or RESP, the BioBank (PADB), the Régie de l'assurance-maladie du Québec (RAMQ) Medication Prescriptions database, and the reMed (Registre de données sur les médicaments) database.	Québec, Canada.	Assessing adherence to inhaled corticosteroids	1): Primary adherence metric 2): Secondary adherence metric was based on PDC in subjects who filled at least one prescription.	Primary adherence = filling the ICS prescription at a pharmacy within 12 months.	The use of PDC as a unique measure could lead to substantial overestimation in adults. An integrated measure of primary and secondary are recommended.	Using PDC adherence in adults was found to be 36.6% compared to adherence rate of 52.8% when a primary adherence metric is used.
Covvey et al[55]	The study included Patients with physician Diagnosed asthma or COPD who received inhaled therapy (10,177 patients with asthma were included).	A retrospective study	A prescribing database from the National Health Service (NHS) Forth Valley Airways Managed Clinical Network in coordination with the E-PRS clinical recording tool program (Campbell Software Solutions©, Irvine, UK)	NHS Forth Valley Scotland, UK	Compare adherence and persistence with inhaled therapies in patients with asthma and COPD	MPR; Persistence with inhaled therapies.	1): MPR = the sum of the days of medication supply provided divided by the total time treated. Mathematically, MPR= (total days of medication supply) ÷ (Days between first and last fills) ×100%. 2): Persistence was determined by employing the Kaplan–Meier survival analysis for time to discontinuation.	NR	Overall median TTD was 90 days (IQR: 50–184 days) for patients with asthma and 115 days (58–258 days, comparison $p < 0.001$) for patients with COPD
Darbà et al[27]	The authors reviewed the medical registries of asthma patients treated with ICS/LABA totaling (n=2213)	A retrospective and multicenter study	Medical registries of asthmatic patients (Pharmacy administrative database and clinical visit data from electronic asthma patient records)	Badalona Serveis Assistencials, Barcelona, Spain	Asthma medication compliance	MPR	MPR was defined as the ratio of the number of days supplied for a given medication to that of the number of days in the study and persistence data.	MPR has been documented to be biased upwards (Price 2013; WHO 2003). The authors tried to correct the bias by elevating the cut-off point so that few patients will be seen as compliant with their medication.	

D'Ancona et al[56]	Ninety-one (91) severe eosinophilic asthma (SEA) patients [with mean age of 53.7] were included.	Retrospective assessment, and prospective follow-up.	NHS sources including Summary Care Records, Local Care Records, GP recording system, and hospital pharmacy dispensing system.	UK	ICS adherence and clinical outcomes in SEA patients	MPR	MPR = the number of doses of ICS issued on prescription divided by expected number. Good adherence was defined as MPR > 0.75, Intermediate adherence (MPR: 0.74–0.51) and poor adherence <MPR = 0.5	MPR is expressed as a function of prescription issued and hence it does not measure directly whether the medication was use or not. This is likely to overestimate ICS use. The adherence cut-off rate adopted was arbitrary although consistent with other studies.	The study found 68% of the patients with good ICS adherence use and 18% with poor ICS adherence. There was a greater reduction in oral corticosteroids (OCS) dose among patients with good adherence.
Delea et al[28]	The study included 12,907 patients (mean age=40 years) with two prescriptions of FSC and diagnosis of asthma.	Retrospective longitudinal analysis	PharMetrics Patient Centric Database	USA	Assessing the association between adherence with fluticasone propionate/ salmeterol combination (FSC)	MPR	MPR was estimated as the ratio of the total number of 'covered days' during the 'treatment period' to the number of days in the treatment period.	NR	Achieving each 25% improvement in adherence was associated with a 10% reduction in the odds of asthma-related ED visit after adjusting for baseline factors.
Feehan et al[29]	The study examined 2193 patients who received controller medications for managing asthma in a 12-month duration including their refill data.	Prospective cohort study	Community pharmacy dispensing database	Utah, USA	Level of adherence to controller asthma medications	PDC, MPR (standard cut-offs of ≥80% medication availability)	PDC, MPR		Approximately 14–16% of the patients had satisfactory adherence over the 6-month follow-up after employing the standard cut-offs of ≥80%.

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Friedman et al[15]	The study analyzed and included 692 eligible adults and young adults aged 12–25 years with diagnosis of mild asthma from the database and assigned an index date based on their first prescription fill.	A retrospective claims analysis	Administrative insurance claims database	United States	Adherence and asthma control	1): Adherence measured by prescription fills and PDC. Refilling prescription on or before the scheduled medication to run out records PDC =1. Inability to refill prescription as scheduled records PDC<1. 2): Asthma control was measured by exacerbations short-acting β2-agonist (SABA) canister claims.	1): Prescription fills: The total number of prescriptions fills during the post-index period. PDC: was calculated by dividing the number of days patients had medication on hand by the total number of post-index days, which in this case was 365 days. 2): Asthma exacerbations: an asthma episode that required hospitalization, treatment in an emergency room, or an outpatient visit in which patients received nebulized medication or a prescription for oral corticosteroids 3): Asthma control: the study measured this by evaluating exacerbations and SABA canister claims.	In calculating Medication Adherence using medical pharmacy records, it is difficult to verify whether or not medication was taken by the patient as prescribed. However, this approach of adherence using the claim approach is objective and could be more representative of the "real-world" than other measures.	During the post index period, compared to the Fluticasone propionate (FP), adherence was significantly higher in the Mometasone furoate delivered through a dry powder inhaler (MF-DPI) cohort (23.5% vs 14.5%; $p < 0.0001$) and prescription fills (2.70 vs 1.91; $p < 0.0001$).
Gelzer et al[30]	The study included 3589 Medicaid members claims that have a primary diagnosis of asthma (ICD-9, 493.xx) and prescription fills for asthma controllers.	Two arm retrospective cohort study with one year follow-up.	Database of Medicaid members with primary diagnosis of asthma.	Two Pennsylvania-based AmeriHealth Caritas MCOs (SEPA and Lehigh-Capital/New West Pennsylvania [LCNWPA])	Effect of interventions on medication adherence and hospitalization rates.	Proportion of days covered (PDC)	PDC is the quotient value of the covered days of asthma medication divided by the days in the measurement period. PDC, with low adherence threshold was (0.20–0.67).	PDC report a more conservative estimate of MA than other measures such as MPR in cases where concomitant multiple medications are used. 2) Avoidance of double counting of days of medication coverage.	Significant improvement in mean PDC rate in both cohorts (+4.9% and +7.2%); p=0.01 and p=0.03, respectively.

Guo et al[31]	The authors selected a total of 299,917 patients with moderate or severe asthma.	A retrospective study	MarketScan Multi state Medicaid database from 2002 to 2007	USA	ICS/LABA medication compliance	ICS-and-LABA MPR	ICS-and-LABA MPR: The sum of day' supply for ICS and LABA drugs divided by the number of follow-up days during the first year after the patient's asthma index date	NR	Average MPRs were 0.23 (median 0.14) for ICSs and LABAs and 0.66 (median 0.46) across all asthma medications within 12 months after asthma index date.
Hagiwara et al[32]	The study included eligible 18,283 patients with an asthma using the ICD-9-CM diagnostic code and 2 or more fluticasone propionate100μg and salmeterol 50μg via Diskus (FSC) or mometasone furoate (MF).	A retrospective cohort study	IHCIS National Managed Care Benchmark Database (Large health insurance claims dataset from January 2004 to December 2008).	USA	Risk of asthma exacerbation; asthma-related healthcare utilization and costs; adherence to controller therapy.	MPR and refill rates were used to measure adherence to controller therapy.	1): MPR: calculated as the sum of the number of therapy-days supplied on all FSC 100/50, MF110 or MF220 dispensed from the index date to the end the follow-up period divided by the sum of the number of days between the first and last such prescription during follow-up and the number of days on the last such prescription. 2): The refill rate: the number of prescriptions for FSC 100/50, MF 110, or MF 220 dispensed from the index date to the end of the follow-up period divided by the duration of follow-up.	Estimate of MPR could be bias (downwardly or upwardly bias) if the patients were instructed to use their medications at a different dosage than implied by the days and quantity supplied information on each claim.	For adherence to ICS therapy, using MPR, the adherence rate for FSC was 27.2% compared to 21.1% in MF. For adherence using the refill rate per year, the adherence rate for FSC was 2.9% compared to 3.1% in MF.
Hardstock et al[33]	A total of 406 patients with asthma were included in the study with mean age pf 55.48 years	A secondary data analysis/ retrospective study.	Primary data collected over 12 months linked to patient-specific claims data (AOK PLUS database).	Germany	The impact of a specific method for measure patients' non-adherence.	Non-adherence (NA) was measured by: 1): MPR 2): Weighted average MPR across different agents. 3): PDC (PDC: day covered if at least one medication was available).	MPR, PDC	NR	The selection or the use of a particular method to measure adherence based on prescription data has a significant effect on the study results.

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Ismaila et al[14]	A total of 19,126 patients, age 12 years with diagnosis of asthma between 2001 and 2010.	Observational single cohort study	Quebec Provincial Health Insurance administrative databases (Re ´gie de l'Assurance Maladie du Que ´bec, RAMQ).	Quebec, Canada	Assessing long term association between adherence and risk of exacerbations.	Adherence measured by: MPR, with cut-off ≥0.80; and persistence (absence of treatment gap ≥ 30 days).	1): MPR: calculated as the percentage of days covered by the medication during the follow up period. Compliance was defined as MPR ≥ 80% and non-compliance as MPR < 0.80. 2): Persistence was defined as having prescriptions of the ongoing therapy continuously renewed without a gap of more than 30 days.	The use of the MPR and persistence measures does not guarantee whether patients actually took their medications.	There was significant reduction in the adjusted odds of exacerbation for the compliant patients and persistent patients.
Kang et al[18]	A total of 22,130 adult asthma patients were eligible for inclusion.	Nationwide population-based observational study	Korean National Sample Cohort database	South Korea	Asthma exacerbation, associated with many risks' factors	MPR	MPR used in the study	NR	High MPR (MPR ≥ 0.50), compared to low MPR (<0.20) showed adjusted ORs of 0.828 (95% CI 0.707 to 0.971) and 0.362 (0.185 to 0.708) in moderate and severe asthma, respectively.
Kelloway et al[34]	The study included 59 patients with mean age 46.7, with diagnosis of asthma.	A retrospective medical chart and pharmacy claims record review	Pharmacy claims data	Minnesota, USA	Effects of addition of salmeterol to a medication regimen on patient adherence.	The rate of adherence for inhaled corticosteroids alone, salmeterol alone, and both salmeterol and ICS were calculated as using % adherence method.	% Adherence = (Medication refilled /Medication prescribed) ×100%	NR	The addition of salmeterol to the ICS did not affect adherence rates to prescription refills for prescribed ICS therapy. There was a higher rate of adherence to salmeterol than ICS at baseline (58.7% ± 28.3%)

Makhinova et al[36]	A total of 32,172 patients with a primary diagnosis of asthma.	A retrospective study	Texas Medicaid claims data	Texas, USA	Adherence to asthma controller medication, risk of exacerbation, and use of rescue agents.	PDC	PDC to asthma long-term controller medication. PDC cut-off used (PDC ≥ 0.80, PDC ≥ 0.70, PDC ≥ 0.60, PDC ≥ 0.50).	NR	Compared to the non-adherent patients (PDC < 0.50), patients who were adherent to the medications (PDC ≥ 0.50) were 1.967 times more likely to have ≥ SABA claims.
Navaratnam et al[35]	16,063 asthma patients (aged 12–65 years) who initiated treatment with Mometasone furoate (MF) or fluticasone propionate (FP) formed the study population.	A retrospective study	Pharmacy claims database from a commercial insurance database	USA	Adherence to MF or FP, mean number of exacerbations, and asthma exacerbation incidence	PDC was used to measure adherence during post-index.	PDC	NR	NR
Papi et al[37]	Asthma patients (n=7195) aged 18 years and older with 2 or more ICS prescriptions were identified from the OPCR database.	Historical cohort study	Optimum Patient Care Research (OPCR) Database and the initiative Helping Asthma in Real People (iHARP) database.	UK (England, Scotland, Wales, and Northern Ireland).	Relationship between ICS nonadherence and asthma exacerbation.	MPR	MPR: the number of ICS prescriptions issued divided by the expected number of ICS prescriptions (based on prescribed ICS dose), MPR > 0.80 is considered adherence to ICS therapy.	These researchers have demonstrated that a wide variety of cut-off values for definition of medication adherence have been employed, the cut-off of MPR > 80% has been employed as an arbitrary standard threshold in the respiratory literature.	Patients who adhered to ICS therapy was not associated with decrease exacerbations of asthma.
Sicras-Mainar et al[38]	2303 confirmed diagnosed asthma patients 15 years and older who initiated ICS treatment.	An observational, retrospective study	Electronic medical records of the Badalona Health Service provider	Barcelona, Spain	To estimate adherence to asthma treatment with inhaled corticosteroid.	MPR, MPR ≥ 80%, = adherent MPR, MPR < 80% = MPR nonadherence	MPR ≥ 0.80, = adherent MPR, MPR < 0.80 = MPR nonadherence	NR	51.0% of patients adhered to treatment.

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Table 1 (Continued).

Author	Population (Adolescent or Adult Asthma)	Study Type	Name of Administrative Health Database	Location	Outcome Assessed/Study Objectives	Medication Adherence/ Related Measures	Definition of the Measure/Method	Strength and Weaknesses/ Limitations of the Measures	Estimated Rate of Adherence Measured/ Study Results
Souverein et al[39]	Individuals with physician diagnosed asthma who had initiated ICS therapy. In all, a total of 13,922 eligible patients (mean age, 39.9 years) were identified	A historical cohort study	Optimum Patient Care Research Database (OPCRD)	UK	ICS adherence pattern. The primary outcome was EMR-based ICS adherence estimated by continuous medication availability (CMA).	Treatment episode length (persistence) and Continuous Medication Availability (CMA1) implementation. The threshold for CMA1 for adherence was CMA1 ≥ 0.80, and CMA II ≥0.80.	1): Treatment episode: defined as a series of successive ICS prescriptions irrespective of switching between different products and changes in dose. 2): CMA implementation: CMA1 (the first method) is also called the PDC which does not take into account the period between the start of the window to the first dispensing or prescription within the window. The CMA II, the second method considers the effect into the observation window as well as carryover within the window and the remaining surplus at the end.	NR	Results not specifically related to rate of adherence or non-adherence.

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Stanford et al[21]	A total 9951 adult asthma patients 18 years and older with at least 15-month continuous enrollment were identified.	A retrospective cohort study	Optum Research Database, a proprietary research database containing enrollment, medical, and pharmacy claims data	USA	Comparing asthma patients' measures of adherence, persistence, and the asthma medication ratio (AMR).	1): PDC-adherence measure (mean PDC ≥ 0.5; PDC ≥ 0.8 2): Persistence and AMR.	1): PDC = (total number of days of medication availability based on filled prescription) ÷ (Length of each subject's observation period). 2): Persistence: The total time between the index treatment/date and the time to discontinuation of the therapy. PDC: used a proxy measure to measure adherence.	NR	A significant proportion of patients on FF/VI achieved a PDC ≥ 0.5
Stern et al[40]	A total of 97,743 asthma patients and with controller medication prescriptions with mean age of 32.8 years were identified and included. Number of patients in the adult age category (18–64) years was n=61,238 and the elderly (65 +) was n=3316.	A retrospective cohort study analysis	PharMetrics database (contains a nationally representative health and billing information)	USA	Examining the association between medication compliance and exacerbation in asthmatic patients	MPR (using the 75th percentile of MPR as the cut-off for adherence), and number of prescriptions for each index medication. MPR was used as a proxy for compliance. Additional cut-off points: patients with at least 2 prescriptions were classified as more compliant than compared to patients with only 1 prescription.	MPR = (the number of days supplied for a particular medication) ÷ the number of days in the study. For maximum MPR, MPR = 1 or 100%. This measure provides information whether the patient is using the right number of medications in a specified time frame.	Researchers indicated that the use of MPR and refill rates as a measure for adherence may reflect appropriate use of inhaler medications. A limitation with the use of MPR is that it makes it impossible to be able to determine with certainty whether the patients were taking their medications as prescribed in the appropriate timely fashion.	The study found more compliant patients as having lesser likelihood of experiencing exacerbation.

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Table 1 (Continued).

Author	Population (Adolescent or Adult Asthma)	Study Type	Name of Administrative Health Database	Location	Outcome Assessed/Study Objectives	Medication Adherence/ Related Measures	Definition of the Measure/Method	Strength and Weaknesses/ Limitations of the Measures	Estimated Rate of Adherence Measured/ Study Results
Svedsater et al[42]	A total of 4327 adult asthma patients initiating FF/VI and BDP/FM were eligible for inclusion into the study population.	A retrospective cohort study	Health Improvement Network (THIN) database	UK	Primary objective was to compare persistence of ICS/LABAs. Secondary objectives were: PDC and proportion of patients with PDC ≥0.50 and ≥0.80	PDC and persistence	PDC and persistence	NR	Median (interquartile range) PDC was 89.2 (61.6–100.0) for FF/VI and 75.9 (50.5–98.0) for BDP/FM ($p < 0.0001$)
Taylor et al[41]	The study included 292,738 asthma patients aged between 12 and 65 years from the period 1997 to 2010.	A retrospective cohort study	Clinical Practice Research Datalink (CPRD) database	UK	Developing annual measure of asthma patients' adherence to ICS use	Adherence to ICS was measured by the annual prescription possession ratio (PPR)	PPR = (Number of days prescribed during calendar year) ÷ (Number of days in the interval) × 100	The PPR employed the prescribing data which makes it difficult to interpret the accuracy of the measure. However, the precision of this metric appeared to be good. The authors concluded that the PPR should be used with caution to determine the actual levels of medication adherence in asthma patients.	The PPR is useful in measuring changes in adherence over time.

Vaidya et al[57]	The study included 277 patients, 18 years and older with persistent asthma	A retrospective, cross-sectional study	Medical Expenditure Panel Survey (MEPS) 2013–2014 data	USA	Determining racial and ethnic disparities with the adherence to inhaled corticosteroids (ICSs) in adults with persistent asthma	Median MPR was used to dichotomize adherence levels	MPR was defined for each patient as the total number of supply divided by the total number of days evaluated. The median MPR was used to categorize adherence into two levels. Asthma patients with adherence levels below the median MPR cut-off were non-adherent to ICS, MPR levels above the median MPR were considered adherent to ICS. The median MPR was 0.25.	Using this metric, researchers were unsure or not able to confirm whether patients used their prescribed medication received as expected. There could be instances where patients filled their medications but did not take them as recommended by their healthcare provider.	The study showed average MPR level as 0.33 among the white race, 0.37 among the African Americans, and the rate among the minorities was 0.35.

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Table 1 (Continued).

Author	Population (Adolescent or Adult Asthma)	Study Type	Name of Administrative Health Database	Location	Outcome Assessed/Study Objectives	Medication Adherence/ Related Measures	Definition of the Measure/Method	Strength and Weaknesses/ Limitations of the Measures	Estimated Rate of Adherence Measured/ Study Results
Vaidya et al[43]	A total of 1447 asthma patients with mean age of 32.27 years were included	A retrospective cohort study (with follow-up)	Medstat MarketScan databases (containing paid medical and prescription drug claims for privately insured patients)	USA	Adherence to controller drugs	MPR	MPR calculated as the number of days of a given medications supplied divided by the number of days in a specified time frame. The authors computed the MPR for dual-controller medications by finding the average MPR values for individual controller medications (ICS and LABA or LTRA). The median MPR was set as the cut-off point to categorize patients into either more adherent group or less adherent group. This study computed MPR by dividing the number of the number of days of medication supply during the 6-month follow-up period by 180.	There is no ideal threshold for measuring adherence to prescription medications in the literature. An arbitrary threshold of MPR (0.7 or 0.80) has been used by many researchers in the literature. Using the median as the cut-off point could avoid variation in the results when different thresholds are used.	A significant association was observed between increasing risk of non-adherence to medications and increased level of cost sharing among asthma patients on dual-controller medications.

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Van Boven et al[44]	A total of 3062 new users of ICS/LABA FDC with diagnosis of asthma were identified.	A retrospective cohort study	Australia subsidized via the national Pharmaceutical Benefits Scheme (PBS) database	Australia	Trajectory analyses of adherence patterns in asthma patients	Group-based trajectory modeling (GBTM)	Patients' adherence to ICS/LABA FDC was estimated using the GBTM over 1 year duration from index-date. The GBTM first identifies clusters/groups of asthma individuals with similar trajectories (eg, Dispensing patterns) using maximum likelihood method.	The GBTM is an alternative method to PDC and it overcome the limitations of PDC of being unable to provide information about the longitudinal course of adherence to treatment over time.	For adherence trajectories, the rate of non-persistent use was 20%, seasonal use was 8%, poor adherence was 58% and good adherence was recorded as 13%.
Vervloet et al[46]	A total of 10,472 asthma patients were included	A retrospective study	Optimum Patient Care Research Database (OPCRD)	UK	investigating the relationship between ICS implementation and asthma-related outcomes over 2 years	ICS implementation/ adherence	ICS implementation defined as the percentage of days covered by the prescription on the basis of quantity, dosage and duration	ICS implementation ranges from 1% to 99%	ICS implementation in the preceding interval was not predictive of risk domain asthma control.
Williams et al[45]	A total of (9706 BFC and 27,975 FSC) asthma patients aged 12–64 years with 1 or more pharmacy claim for ICS/LABA were included.	A retrospective analysis	HealthCare Integrated Research Database	USA	Evaluating the association between patients' adherence to prior asthma controller medication and choice of therapy initiation.	MPR (the study assessed MPR for monotherapies such as ICS, LABA, leukotriene receptor antagonist [LTRA], theophylline, omalizumab), and combination therapies (ICS +LABA, ICS+LTRA, and LABA+LTRA)	A composite weighted MPR measure was computed ranging from 0 to 1 based on the percentage of time each medication was used. MPR > 0.80 indicated patients' adherence to the therapy,		Adherence to previous use of controller therapy was similar between the two groups.

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Table 1 (Continued).

Author	Population (Adolescent or Adult Asthma)	Study Type	Name of Administrative Health Database	Location	Outcome Assessed/Study Objectives	Medication Adherence/ Related Measures	Definition of the Measure/Method	Strength and Weaknesses/ Limitations of the Measures	Estimated Rate of Adherence Measured/ Study Results
Williams et al[61]	298 participants aged 12–56 years (mean age=34.5) in the Study of Asthma Phenotypes and Pharmacogenomic Interactions by Race ethnicity (SAPPHIRE).	A prospective asthma cohort study/ retrospective study	Data from SAPPHIRE study linked with Pharmacy claim data	USA	Measuring changes (ICS) adherence over time	MPR related measure. More than (MPR>0.75) was associated with reduction in exacerbation.	Estimated as the cumulative days' supply divided by the number of days of observation (ie, a moving 6-month observation period for the current study).	Their method accounted for (prorated) prescription refills. This is because prescription refills partially overlapped with the beginning and end of each observation period and incorporated when a medication was discontinued by a physician.	Achieving more than 75% adherence was associated with reduction in exacerbation. An estimated 24% of asthma exacerbations were attributable to ICS medication non-adherence.
Woodcroft et al[48]	The study identified and included 5256, with persistent asthma patients with mean age of 30.4.	A retrospective study	Integrated Healthcare system database	Detroit, USA	Assessing adherence to ICS ±LABA and rate of exacerbations	PDC; Exacerbation: defined as oral corticosteroids fill dispensed within 2 weeks after primary diagnosis of asthma.	PDC	NR	The study found adherence rate to ICS ± LABA to be low with high rate of exacerbations.

Wu et al[47]	The study included 69,652 patients with persistent asthma with mean age of 37 years.	A retrospective cohort study	Population Based Effectiveness in Asthma and Lung Diseases (PEAL) Network	USA	Comparing adherence to controller medications for asthma	Four (4) measures of adherence on each of ICS, LTRA, ICS/LABA were studied. 1): Primary adherence 2): early-stage persistence 3): adjusted PDC (dichotomized as PDC < 0.75, and PDC ≥ 0.75) 4): Mean adjusted PDC	1): Primary adherence: Was determined whether or not the prescription was filled within 30 days. 2): Prescriptions filled within 30 days and between 31 and 180 days after provision of prescription. 3) Adjusted PDC which employed the use of an index date based on the date of the first prescription than the date of the fill.	1): The authors employed a combined data on prescriptions from providers and fills to determine what they claim as a more accurate measure of adherence rather than using only medication dispensing data. 2): One common limitation was the fact that all the adherence metrics were based on an electronic and hence makes it difficult to determine whether individuals took their dispensed medications.	Using PDC as a measure, the study recorded improved adherence for LTRAs and ICS/LABAs than using ICSs.
Zhang et al[49]	The study population included 9716 patients 12 years and older (mean age =47.09 years) with diagnosis of asthma and severe asthma.	Observation cohort study	Quebec Health Insurance administrative databases	Quebec, Canada	Impact of adherence and exacerbation frequency on healthcare utilization and direct cost	Overall MPR (MPR ≥ 0.80)	Overall MPR	NR	For every year, the non-adherent patients' healthcare was more costly than the adherent patients.

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remaining articles were mostly performed in Europe (Netherlands = 1, Denmark = 1, Spain = 2, United Kingdom (UK) = 8, Germany = 1 and France = 1) and one study each were conducted in South Korea (n = 1) and Australia (n = 1).[18,27,33,38,39,41,44,46,51,55,56,63–65] The study population consisted of 1,001,662 adolescents and adults with physician diagnosis of asthma in any population-based administrative database. More than one-third (n = 13) of the studies observed adherence and clinical outcomes (ie, asthma exacerbation, emergency room visits) simultaneously-[14,15,17,18,28,30,31,34,37,40,45,48,56] while three studies assessed the association between medication adherence and cost of asthma.[43,49,57] The occurrence of the targeted clinical outcome was assessed from 12 months to 10 years.

In view of this, the various asthma databases employed were of great interest in this review. As reported in Table 1, majority of the administrative databases used were pharmacy claim databases capturing patients' medical records, prescription refills and records of drugs dispensed. Notable among them were the pharmacy claim databases from the IQVIA™ Health Plan Claims Data, Danish Registry of Medicinal Product Statistics, HMO-claim records/database, Quebec Provincial Health Insurance administrative databases, Maintenance et Exploitation des Donnees pour l'Etude de la Clientele Hospitaliere (MED-ECHO), Québec prescription claims databases, Optimum Patient Care Research Database (OPCRD), Administrative insurance claims database, Medstat MarketScan database, and Clinical Practice Research Datalink (CPRD).

Measures of Medication Adherence

The assessment of medication adherence varied across studies. This review identified 20 different metrics used in measuring medication adherence in asthma patients. Some of the reported measures were medication possession ratio (MPR), proportion of days covered (PDC); Continuous Measure of Medication Acquisition (CMAq), proportion of prescribed days covered (PPDC); Persistence with inhaled therapies; Continuous Medication Availability (CMA), Refill Rate, Annual Prescription Possession Ratio (PPR); Group-Based Trajectory Modelling (GBTM) and others (see Tables 1 and 2). The MPR and PDC were commonly reported as the primary measures of medication adherence. Thus, approximately 87% of the included studies reported the use of both PDC and MPR as the main/primary metrics for asthma patients' medication adherence in the long term. Specifically, 20 studies (53%) employed MPR and 13 (34%) used PDC as a measure of medication adherence. The majority of studies chose a fixed time-frame for the refill interval than using the last refill as the endpoint for the refill interval and did not exclude the last refill in the estimation of MPR. Additionally, some studies[14,21,29,47,52,55] adopted multiple asthma adherence metrics (specifically: Med-Total and MPR; MPR and persistence; PDC and MPR; Prescription fills and PDC; Refilling and PDC; and MPR and persistence metric). Modifications of the two commonly reported measures (MPR and PDC) were also reported. Blais et al[54] developed the annual proportion of prescribed days covered (PPDC) method as a modification of the PDC measure. The PPDC has the ability to account for prescribing patterns used in the administrative databases. A number of studies reported the continuous measure of availability as adherence metric which is an MPR calculated across multiple refills.[37,61] Hardstock et al[33] and Visaria et al[62] compared the weighted average MPR and adjusted MPR to other measures in identifying non-adherent asthma patients.

Definition/Equation of the Adherence Measures

There was variation in the definition and calculation of the two commonly reported adherence measures – MPR and PDC. With regards to the MPR-related measures, the denominator of the MPR formula varied from study to study. For instance, the majority of the studies estimated MPR as the sum of the days' supply for medication fills divided by the time from the first supply fill until the end of the measurement period.[19,27,31,40] Similarly, MPR was calculated in other studies as the sum of days of medication supply divided by the total time treated or evaluated.[55,57] Other adherence calculations of MPR adopted a fixed denominator within the year representing the days between the first and the last refill. In a study by Martin et al,[60] MPR was computed as the sum of the number of days' supply of inhaled corticosteroids (ICS) divided by 365 days and multiplying the overall expression by 100% to provide an adherence percentage value. Measures such as the Med-Total, Medication Refill Adherence (MRA), and Continuous (Multiple Interval Measures of) Medication Availability (CMA 4 and 7) used formulae similar to MPR definitions.

The MPR fixed interval is generally applied for assessing seasonal use of medication as well as for assessing medication use in patients with allergies.[66] The MPR takes a range of positive values from 0 inclusive through to "at least 1". A zero MPR denotes no adherence, while an MPR value of 1 measure optimal adherence. In some extreme cases, an MPR above one shows that the patient took more than prescribed medication, while MPR value

Table 2 Distribution of the Adherence Metric Reported by the Included Studies

ID	Adherence Metric and Related Measures	Number of Studies	Reference
1	Medication possession ratio [MPR] (weighted average MPR, adjusted MPR, MPR using CMAq4 and CMAq 7)	22	[14,18,19,27,29,31–33,37,38,40,43,45,49,52,55–57,60,62,64,65]
2	Proportion of days covered [PDC]- (mean adjusted PDC, adjusted PDC)	14	[15,21,29,30,33,35,36,42,47,48,50,51,53,59]
3	Medication total [Med-Total] (proposed by Steiner et al)	1	[52]
4	Medication Out [Med-Out]	1	[52]
5	Suissa et al measure of regularity of inhaler refills	1	[52]
6	Continuous Measure of Medication Acquisition (CMAq7), (CMAq4), (CMAq7)	1	[63]
7	Asthma medication ratio (AMR)	2	[19,21]
8	Proportion of prescribed days covered [PPDC]	1	[54]
9	Concordance for days' supply	1	[58]
10	Concordance for the refills allowed	1	[58]
11	Monthly cumulative proportion of canisters dispensed	1	[52]
12	Persistence with inhaled therapies/early-stage persistence (ie, Length of treatment episode)	6	[14,21,39,42,47,55]
13	Refill rate	1	[32]
14	Percentage (%) adherence method	1	[34]
15	Continuous Medication Availability [CMA]	1	[39]
16	Annual prescription possession ratio (PPR)	1	[41]
17	Group-based trajectory modeling [GBTM]	1	[44]
18	ICS implementation/adherence	1	[46]
19	Primary adherence metric	2	[47,53]
20	Prescription fills	1	[15]

below 1 indicates less than prescribed medication within a specified period.[67]

Similar to MPR, there were variations in calculation of PDC-related measures in majority of studies estimating the PDC as a quotient value of the days covered divided by the days in the measurement period. It was also estimated as the percentage of days a patient had access to medication depending on the amount of medication obtained. A fixed interval PDC was calculated as the ratio of the number of days a patient had medication on hand to the total number of post-index days (ie, 365 days).[15,21,29,30,33,35,36,42,47,50,51,53,59]

Three studies assessed medication adherence using the CMA measure with slight variations in formulae.[17,39,45] The CMA was calculated as the cumulative days' supply obtained over a series of intervals divided by the total days from the beginning to the end of the time period in the study. The overall average of all participants' CMA provided the adherence value of the entire time period of the study and evaluates the relationship of adherence and drug effect. It has been suggested that the CMA and MPR as well as Medication Refill Adherence (MRA) provide identical adherence measuring power.[17,39,45]

The AMR was calculated as the ratio of units of controller medication to the sum of units of controller medication and rescue medication. Two studies–Bidwal et al[19] and Stanford et al[21] –assessed medication adherence with the AMR metric and further evaluated the

impact of treatment groups on adherence among adults with persistent asthma.

Six studies assessed persistence as another measure of medication adherence which was estimated as the total time between index treatment/date and time to discontinuation of the therapy.[21,42,47,55] Several variations in calculation of persistence were reported among included studies.[14,21,39,42,47,55] While drug persistence was calculated based on prescriptions filled within 30 days and between 31 and 180 days after provision of prescription in some studies,[39,42,55] others estimated persistence based on the absence of treatment gap '≥30′ days.[14] Table 1 gives a detailed description of the formulae and equations for the remaining adherence methods.

The Continuous, Multiple Interval Measure of Medication Gaps (CMG) measures were used in only one study[45] to assess level of adherence and the impact of treatment on adherence. According to Williams et al, the CMG was obtained by dividing the total number of days in treatment gaps by the duration of the time period of interest in order to recognize any time intervals without drug exposure. Any negative value was set to 0. The CMG essentially calculates nonadherence values for cumulative periods without considering the possibility of early refill or overfill.[17]

Adherence Measures and Cut-Off Value (Threshold)

In this review, studies used various cut-off values or thresholds to estimate level of medication adherence among adolescents and adults. For MPR, the cut-off values or thresholds for good/high medication adherence ranged from '>0.75 to >1.00′ (See Table S8 in the Supplementary Material). Adherence metrics identified in this review were commonly categorized into two or more levels during assessment and for testing associations with study outcomes. The cut-offs or thresholds distinguish adherence and nonadherence or adherence from partial adherence. Categorizing adherence metrics into two distinct levels (adherence vs non-adherence) was common observation among most of the studies. Among studies which dichotomized adherence score, ten (10) assessed adherence using MPR, seven (7) with PDC, two (2) assessed adherence with AMR and one (1) employed the CMA measure. An arbitrary cut-off value or threshold of '≥0.80′ was commonly employed in most of the studies for both MPR and PDC.[14,19,37,38,45,49] The adherence cut-off value for AMR measure reported in this review was >0.50.[19,21] Four studies categorized adherence metrics into three or more categories. They were either categorized based on arbitrary cut-offs/thresholds or around suitable quintiles of the adherence scores. A study by Bidwal et al[19] set the cut-off point for good adherence at MPR ≥ 0.80, medium at MPR ≥ (0.5–0.80) and low at MPR < 0.5: compared to D'Ancona et al[56] study with adherence levels; good adherence (MPR > 0.75), intermediate (MPR: 0.74–0.51) and poor (MPR ≤ 0.5). Good adherence cut-off value for the PDC ranged from at least 0.50 to 0.80 and considered any value <0.5 as non-adherent. Three studies estimated adherence thresholds by computing median and 75th percentile of the adherence scores[40,43,57] and the values above the medians denoted good or high adherence cut-off value. In the same vein, adherence scores ≥1 denoted optimal and excess adherence [see Tables S3 and S8]. Only two studies assessed adherence and the impact of treatment groups or covariates on it as a continuous variable.[30,45] Thus, researchers did not set adherence cut-off.

Adherence Threshold Determination

Several methods were used to model or link clinical outcomes and adherence rates or determine adherence rates and their determinants in the retrieved articles. Seven studies used descriptive and unadjusted analytical methods to link the various clinical outcomes and adherence rates.[29,32,51,53,54,56,58] The remaining studies employed a wide range of statistical methods to determine the adherence cut-offs as well as link the adherence rates to targeted clinical outcomes. The statistical methods ranged from simple to more advanced adjusted regressions. Logistic regression analyses (binary and multivariate) were used to assess the association between adherence and a range of clinical outcomes including asthma hospitalizations, emergency department (ED) visits and asthma exacerbation in some of the studies.[19,31,36,37,40,55]

Studies using logistic regression compared the odds ratio of different adherence rate groups for asthma related ED visit or for asthma-related hospitalization[14,31] or intubation or all-cause hospitalization[14] or short acting-beta 2 agonist (SABA) use[14,37] or asthma exacerbation.[40] A combination of advanced statistical approaches such as propensity score with various survival analysis, and multivariate generalized linear models were used in examining association between adherence thresholds and various targeted outcomes (see Table S9).

For propensity score with survival analysis, log rank statistics generated two adherence groups that separated most significantly either by shifting the threshold and

comparing the resulting dichotomized adherence groups or risk of discontinuation.[21,50] Adjusted Poisson regressions were employed to determine adherence thresholds or cut-offs and their associations with targeted clinical outcomes in two studies.[45,49]

Meta-Analysis for Threshold Determination

In addition to the narrative/qualitative synthesis, we performed meta-analyses to quantitatively summarize the effect estimates [odds ratios (OR)] for asthma exacerbation associated with specific adherence thresholds. The meta-analysis (Figure 2) focused on the MPR adherence thresholds and asthma exacerbation. The forest plot was sub-grouped into 3 MPR adherence thresholds ("0.75–1.00", "0.5", and "mean/median/75th percentile of MPR value"). Using inverse variance random effects model, we found a significant association between achieving a '0.75–1.00' range of MPR adherence thresholds and reduction in asthma exacerbations with pooled effects estimate [odds ratio (OR): 0.56; 95% confidence interval (CI): 0.41–0.77]. The pooled effect size was heterogenous across the included studies with I^2 = 74%. Similarly, achieving an MPR adherence threshold of "0.50 or more" was associated with lower risk of asthma exacerbations [OR = 0.71, 95% CI = (0.54–0.94)] with I^2 = 65%. In summary, patients who achieved an adherence threshold between '0.75 and 1.00' reduced their risk of exacerbation by 44% compared to those with a cut-off value less than 0.75.

Further, we employed meta-regression to identify the source of the between study heterogeneity. We identified "differences in adherence thresholds", "different study locations", and "varied study durations" as the main sources of the study heterogeneity in the meta-summary analysis (See Tables S4 and S5 in the Supplementary Material).

Publication Bias

The Eggers test recorded a t-statistics of 0.0096, Egger's regression intercept of 0.051 with 95% confidence limits of (−12.04 to 12.15) indicating no substantial publication bias in this review (See Table S6). The study was limited to smaller number of studies included in the meta-analysis for estimating the pooled effect of asthma exacerbation among adherent and non-adherent asthma patients. Thus,

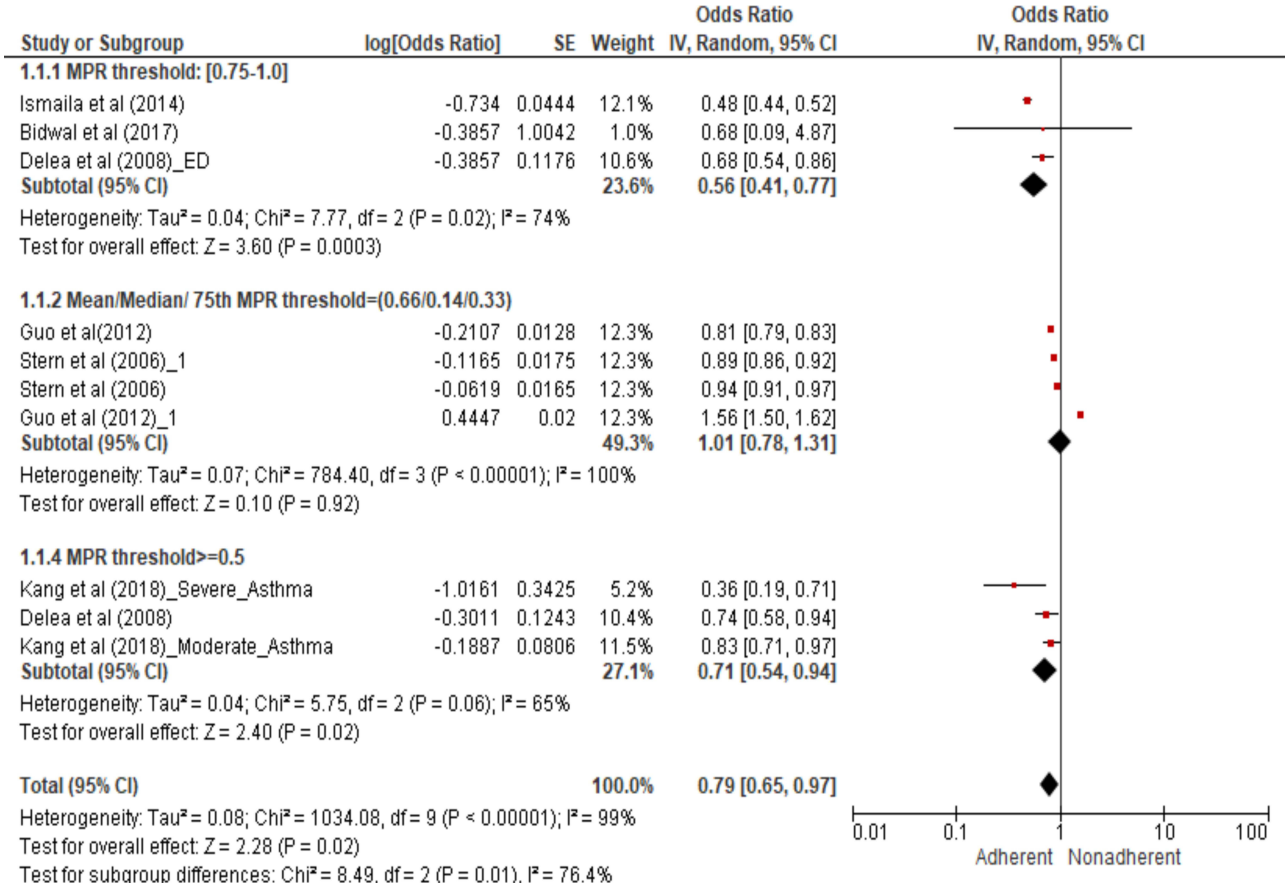

Figure 2 Forest plot of the association between achieving specific MPR adherence thresholds and risk of asthma exacerbations.

resulting in a wider confidence interval with unprecise estimate for the Eggers test intercept. Also, the Fail-safe N test and the funnel plot showed no substantial publication bias. (See Table S7 and Figure S1 in the Supplementary Material).

Outcomes and Adherence Cut-Off/Threshold

The prevalence of nonadherence to asthma medications varied with adherence cut-offs/thresholds set by retrieved studies. Seven (7) studies reported data on adherence prevalence or reported some data which enabled estimation of medication adherence prevalence. With AMR cut-off of >0.50, non-adherence prevalence was the least and ranged from 10.7% to 34.6% (See Table S9 for detailed estimates of adherence prevalence on all 7 studies in the Supplementary Material). While some lower thresholds were associated with improved targeted outcomes of asthma[18,29,37,41,55,61] it appears there is a trend which shows that adherence thresholds of at least 0.50 for MPR, PDC, CMA and AMR could result in significant reduction in asthma-related ED visits, asthma-related hospitalization, and SABA use.

Quality Assessment

Using the Joanna Briggs checklist for cohort studies, we performed quality assessment on all 38 studies included in the review. Overall, studies were evaluated to have a low to medium risk of bias with good methodological quality (see Table S2 in the Supplementary Material). Overall, confidence in the evidence from the reviews of the quantitative research ratings of the included studies was moderate (see Table S2a in the Supplementary Material).

Discussion

This review provides evidence of medication adherence measures in adolescent and adult asthma using administrative health databases. A total of 38 retrospective cohort studies were eligible for inclusion in this review using a stringent criterion. We observed low to medium overall risk of bias across the included studies with a substantial good methodological quality. Overall, a total of 1,001,662 adolescents and adults with physician diagnosis of asthma were included in this review. The authors identified 20 medication adherence measures from the various asthma databases. The measures were calculated using pharmacy claims databases comprising dispensed medications and refill records.

Data on prescription refills offer information about possession of medication and does not necessarily provide details of the actual use of the drug. Hence, information on the prescription refills provide a rough estimate of the adherence and probable overestimation of patients' adherence.[10] The use of administrative data for assessment of medication adherence has limitations which include inability of researchers to confirm whether or not the patients have actually ingested their prescribed medications. Also, the administrative health databases does not always capture detailed patient data including their physical examinations, clinical outcomes and laboratory tests.[14] In spite of these limitations, adherence measured from administrative data has widely been demonstrated to correlate well with objective adherence measures and with clinical outcomes in various disease conditions. There is also documented evidence demonstrating concordance between healthcare database adherence rates and rates estimated from objective measures of adherence such as pill counting, and electronic monitoring.[68,69] In particular, adherence measured from administrative data has been shown to improve clinical outcomes such as asthma exacerbation and highly sensitive in predicting improved asthma outcomes and reflects real-life situation of medication use.[11] Additionally, the International Society for Pharmacoeconomics and Outcome Research (ISPOR) working group has proposed both the MPR and the PDC for measuring medication compliance in claim databases while the Pharmacy Quality Alliance (PQA) has recommended the PDC as the preferred method for assessing adherence for use in their Medicare Star Ratings.[70] Moreover, the administrative electronic health databases are easy to use, linkable to other health databases, and inexpensive in assessing adherence to prescribed medications in patients with asthma.[71]

The MPR and PDC were the two commonly reported methods (representing 87% of the included studies). We found some evidence of subtle distinction in the operationalization of the MPR and PDC measures. For instance, the PDC numerator measured the sum of days of medication covered and MPR numerator measured the sum of days of medication supplied. A cut-off value is advised for the adherence measures in classifying patients' as being adherent or non-adherent.[72,73] Majority of the studies reported threshold for good adherence for the MPR-related measures as '≥0.8′ and the PDC-related measures ranged from at least "0.5 to (≥0.80)" [See Table S3]. To identify the optimal threshold capable of reducing important

clinical events in asthma patients, we linked the varying thresholds ("0.5", "0.75–0.80" and "median/75 percentile MPR thresholds") to a clinical outcome of interest (asthma exacerbation). In particular, we found significant association between achieving MPR threshold of "0.5–1.00" and reduced risk of asthma exacerbation. The use or choice of thresholds between "0.75–1.00" and "≥0.50" were capable of ensuring good asthma control with a reduced asthma exacerbation (OR: 0.56, 95% CI: 0.41–0.77) and (OR: 0.71; 95CI: 0.54–0.94), respectively. The choice of the optimal adherence threshold was based on the cut-off value that reduced asthma exacerbation to a larger extent. Here, patients who achieved a threshold from "0.75–1.00 were 44% less likely to experienced asthma exacerbation compared to adherence rates less than 0.50. Also, individuals who attained an adherence value of at least 0.5 reduced subsequent exacerbations by 29% compared to less than 0.5. Thus, achieving an adherence threshold within "0.75–1.00" is optimal in reducing important clinical events in asthma patients.

The PDC is known to provide a more conservative estimate of medication adherence compared to other measures in cases of concomitant multiple medication usage.[30] It is recommended for assessing medication adherence of patients on multiple therapies as compared to the MPR measure. This measure is also capable of avoiding double counting of days of medication coverage when two refills overlap. Additionally, the PDC provides a more accurate representation of medication adherence because it eliminates the possibility of being unreasonably elevated as it does not include possibility of overlapping days such as refilling a medication early. Major groups and institutions including the Pharmacy Quality Alliance recommend the use of the PDC measure for assessing medication adherence of patients on multiple therapies at the same time.

On the other hand, the MPR is unable to cover multiple therapies and it is mainly used for measuring single medication use. One of the strengths of the MPR measure is ease of accessibility and low-cost.[74] Even though, the MPR is widely used in assessing adherence in most chronic disease medication intake, there exist some limitations associated with it. The MPR is estimated as a function of prescription issued and does not directly measure patients' usage of the prescribed drug or medications. The MPR measures the total days of supply of medications from all medication records over a period for adherence calculations. As a result, it leads to double counting the days patients refill their medications before the previous prescription runs out. This drawback is likely to overestimate the usage of some maintenance medications such ICS. Also, the MPR is likely to cause a downward or upward bias,[75] if patients were instructed to use their medications at a different dosage than implied by the days and quantity of supplied information on each claim.[32]

A common limitation using administrative filled claim databases for adherence calculation was the inability to determine whether the medication was ingested by the patient. Also, the definitions of the common methods (namely MPR and PDC) reported by some studies differed slightly from each other. Notwithstanding, most of the studies reportedly used almost the same definition for the calculation of MPR and PDC measures.

Also, adherence measures do not include medication usage during inpatient visits and hospitalizations due to limitations such as incomplete coverage of some databases. When patients pay out-of-pocket to obtain refills from multiple pharmacies and do not submit an insurance claim, administrative claim databases could be incomplete and limited.[71] We believe that if the patient records in an administrative database are complete (by accounting for patients' likelihood of obtaining medications from pharmacies not captured in the database), the derived methods can be considered to have a high sensitivity.

In choosing an adherence measure using asthma databases, some general issues should be considered and addressed. The measurement of adherence over a short period of time is likely to be imprecise due to unplanned circumstances–hospitalizations–which may be unrelated to adherence. Andrade et al[12] recommended adjusting for the measure of adherence for the hospitalized patients after determining the number of days the patient was hospitalized.

Conclusion

This review identified two commonly reported measures – MPR and PDC – for measuring medication adherence in adolescents and adults with diagnosis of asthma. Other measures identified for measuring the various divisions of adherence included: persistence, Multiple Interval Measure of Medication Gaps (CMG), medication implementation/adherence and prescription fills. Using meta-analysis, we identified an adherence threshold of at least 0.75 as optimal for achieving targeted clinical outcomes such as reduced risk of asthma exacerbation. These measures were found to be consistently used in assessing adherence among asthma patients in administrative claim

databases. While we admit that adherence measures assess medication acquisition rather than ingestion, the identified measures were highly sensitive with a complete coverage of patients' medication records in the database. Despite their limitations, the two database adherence measures are objective and reflect medication use in real-world setting. Future studies should investigate in detail medication adherence thresholds (considering varying thresholds) in relation to asthma clinical outcomes using administrative health databases.

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