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The Validity of Diagnostic Algorithms to Identify Asthma Patients in Healthcare

Administrative Databases: A Systematic Literature Review

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Abstract

Objectives: To review the available evidence supporting the validity of algorithms to identify asthma patients in healthcare administrative databases.

Methods: A systematic literature search was conducted on multiple databases from inception to March 2020 to identify studies that reported the validity of case-finding asthma algorithms applied to healthcare administrative data. Following an initial screening of abstracts, two investigators independently assessed the full text of studies which met the pre-determined eligibility criteria. Data on study population and algorithm characteristics were extracted. A revised version of the **Quality Assessment of Diagnostic Accuracy Studies** tool was used to evaluate the risk of bias and generalizability of studies.

Results: Twenty studies met the eligibility criteria. Algorithms which incorporated ≥ 1 diagnostic code for asthma over a one-year period appeared to be valid in both adult and pediatric populations; (sensitivity $\geq 85\%$; specificity $\geq 89\%$; PPV $\geq 70\%$). The validity was enhanced when: 1) the time frame to capture asthma cases was increased to two years; 2) ≥ 2 asthma diagnoses were considered; and 3) when diagnoses were recorded by a pulmonologist. Algorithms which integrated pharmacy claims data appeared to correctly identify asthma patients; however, the extent to which asthma medications can improve the validity remains unclear. The quality of several studies was high, although disease progression bias and biases related to self-reported data was observed in some studies.

Conclusions: Healthcare administrative databases are adequate sources to identify asthma patients. More restrictive definitions based on both asthma diagnoses and asthma medications may enhance validity, although further research is required to confirm this hypothesis.

Key words: asthma, validation, diagnostic algorithms, administrative databases.

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Introduction

Asthma is a major non-communicable disease characterized by variable symptoms of wheezing, breathlessness, chest tightness or cough, and by reversible expiratory airflow limitation (1, 2). With over 334 million individuals affected worldwide, asthma has become an important public health issue and a leading cause of chronic morbidity, especially among children (2).

To inform health policy and advance therapeutic research in asthma and other chronic diseases, healthcare administrative databases have been widely used in epidemiologic studies and post-marketing drug safety and effectiveness research (3-7). These data sources are preferred over more traditional methods of data collection such as questionnaires, as they provide the opportunity to study disease burden and trajectories in large populations, as well as study rare outcomes, including mortality and hospitalizations, using real-world data (8, 9). Additionally, information in administrative databases do not rely on patient self-report, thereby eliminating the possibility of recall bias (10). However, since these data are primarily used for billing purposes and are a by-product of complex and evolving healthcare systems, there is a concern that misclassification of clinical information may introduce bias. In this context, it is crucial to assess the validity of these data sources for research (11).

Identifying a sample of patients in whom asthma has been diagnosed as accurately as possible is arguably one of the most important first steps in conducting rigorous epidemiologic research (12). In an effort to assess the value of healthcare data for secondary research on asthma, Nissen *et al.* conducted a systematic review on the current methods used to validate asthma diagnoses in electronic health records (EHR) (13), while Sharifi *et al.* reviewed validation methods to capture asthma exacerbations in administrative data (14). To the best of

our knowledge, the validity of the existing asthma diagnosis case definitions applied to healthcare administrative data have not yet been synthesized. Indeed, the past two decades have witnessed an explosion in asthma research conducted using healthcare administrative data and it is crucial to identify the case-finding algorithms which have a better overall performance in terms of distinguishing individuals who actually have asthma and those who do not. The aim of this study was thus to conduct a systematic literature review to identify studies that have validated asthma case-finding algorithms applied to healthcare administrative data. A critical appraisal of each study was conducted alongside to assess potential sources of bias and generalizability of findings. Our hypothesis is that healthcare administrative databases are an adequate source to capture asthma cases.

Methods

This study is among a series of systematic reviews of validated methods for identifying various chronic diseases using healthcare administrative data that have been conducted by the Quebec Strategy for Patient-Oriented Research (SPOR) Support Unit, as part of its mandate to implement strategies to facilitate access and use of health data.

Search strategy and selection criteria

To identify relevant articles, we searched the following databases from their inception to November 8, 2018: Medline; PubMed; Embase; CINAHL; AgeLine; PsycINFO; Abstracts in social gerontology; and all Evidence-Based Medicine Reviews (EBM) Reviews. The search strategy encompassed the following concepts: 1) asthma (and related terms such as bronchospasms); 2) validity (specificity, sensitivity, positive predictive value (PPV), negative predictive value (NPV), and receiver operating characteristic (ROC) curves); and 3) healthcare administrative data. Search strategies were developed in collaboration with a librarian and were

adapted to each database. The Scopus database was used to update the search on March 2020 through a similar search strategy that was validated by a librarian. A complete list of search terms is found in the electronic supplementary files (Table S1).

For this systematic review, we included studies which: 1) applied at least one asthma diagnostic algorithm to healthcare administrative data; 2) validated the algorithm definition(s) against a reference standard; 3) reported at least one of the following key measures of diagnostic accuracy: sensitivity, specificity, PPV or NPV. Studies were excluded if only kappa values were reported or if regression models were used to identify asthmatic patients. Studies which only reported algorithms that combined asthma and chronic obstructive pulmonary disease (COPD) codes were excluded.

All titles and abstracts were independently screened by two investigators, with the aim of identifying original research papers which fit the pre-specified eligibility criteria. All abstracts identified by either reviewer in the abstract screening phase were then assessed in full text. Disagreements of eligibility were resolved by a third reviewer. As a complement to the systematic review, bibliographies of included articles were manually searched for additional pertinent articles, and those articles were subsequently screened and reviewed using the same method (snowballing) (15). The grey literature was also searched to broaden the scope to more relevant studies and provide a more complete view of available evidence.

Data Extraction

For each retained study, a reviewer extracted the relevant information using a standardized data abstraction form. A second reviewer validated the extracted information by the first reviewer and disagreements were resolved by consensus or by a third reviewer, when necessary. Data elements of interest included: 1) study characteristics (author, year, country); 2)

population characteristics (sample size, eligibility criteria); 3) name of administrative database; 4) diagnostic algorithm; 5) reference standard used to identify asthma cases and non-cases; and 6) measures of diagnostic accuracy.

Quality assessment

The **Quality Assessment of Diagnostic Accuracy Studies** revised tool (QUADAS-2) (16) was used to assess risks of bias and generalisability for each eligible study. Based on the recommendations of Whiting *et al.* (2011) (16) and taking inspiration from the systematic reviews on validated algorithms conducted by Woodfield *et al.* (17), Tan *et al.*, (18) and Van Mourik *et al.* (19), the QUADAS-2 was specifically adapted for case identification algorithms in healthcare administrative databases. Details of the quality assessment domains and criteria are presented in the supplemental file.

Results

The literature search yielded 1019 citations. The number of references assessed and reasons for exclusion are shown in Figure 1. After excluding duplicates, 645 abstracts were reviewed and 62 articles were selected for full-text review. The literature review update resulted in 95 additional citations, of which three were retained for analysis. In total, twenty articles met the eligibility criteria and were retained for analysis; fourteen of which were identified through the electronic database search, and six of which were identified via snowballing (n=5) or the grey literature (n=1).

Study and population characteristics

Table 1 provides an overview of the characteristics of the retained studies. The majority were conducted in Canada (n=8) (12, 20-26) and in the United States (n=6) (27-32); other studies

were performed in Italy (33-35), Australia (36), Denmark (37), and the United Kingdom (38). A total of five studies were conducted in pediatric populations (22, 25, 27, 31, 37), seven in adult populations (20, 21, 26, 29, 32, 36, 38), and the other studies included pediatric, adolescent or adult populations (12, 23, 24, 28, 30, 33-35). Among studies which restricted their populations to adults, some studies focused on specific population segments, including women delivering live born infants (32), geriatric individuals (26), patients with multimorbidity (36), and patients who underwent a colectomy (38). The studies were published between 2000 and 2019 and reported on study populations identified between 1994 and 2017.

Quality assessment

Several studies had a good methodological quality. However, studies which used surveys, questionnaires or interviews as the basis for the reference standard (n=7) have potentially introduced bias related to self-reported data, including misclassification bias. Moreover, the validity of several algorithms tested in pediatric populations may have been hampered by the disease progression bias (22, 23, 25, 28, 31, 33-35), which arise when the patient condition changes between administering the index and reference test (39). The quality assessment domains, criteria and results are shown in the supplementary files (Table S2; Figure S1).

Reference standards

In adult populations, reference standards used to distinguish asthma cases from non-cases consisted of clinical case definitions involving: 1) documentation of diagnoses in medical charts, reviewed by either trained chart abstractors or research nurses (12, 30, 32, 38); 2) adjudication of asthma by a physician using the criteria specified in the Expert Panel Report of Guidelines on Asthma (29) or clinical criteria involving a combination of documented diagnoses as well as patient history of wheezing and shortness of breath (33); and 3) patient self-reported data from

surveys (21, 23, 36). For pediatric asthma, reference standards included: 1) review of diagnoses documented in medical records by trained chart abstractors or research nurses (12, 27, 35); 2) pediatric allergist-diagnosed asthma (22); 3) review of medical charts by a general pediatrician and a pediatric respirologist using clinical criteria based on documented episodes of wheezing and response to asthma medication (24, 35); and 4) parent report of a physician diagnosis of asthma, wheezy cough or reactive airway disease through telephone interviews or questionnaires (25, 28, 34). Furthermore, one study sent out, for each child with no discharge diagnosis of asthma recorded in their medical chart, a questionnaire to the general practice clinic where the child was registered at the time of the study to further confirm absence or presence of asthma diagnosis (37).

Summary of algorithms and validity

Table 2 and 3 provide details of the algorithms reported in each publication, according to whether studies used, respectively, clinical/chart review (n=13) or self-reported data (n=7), as the basis for the reference standard. Of note, meta-analysis was not conducted due to substantial heterogeneity found in the studies with respect to study characteristics, types of reference standards used, and diagnostic accuracy measures reported.

The majority of studies developed and tested asthma diagnostic algorithms as the primary research question, while eight reported on the validity of other diagnoses as well, most commonly COPD (22, 23, 26, 29, 32, 33, 36, 38). Most studies constructed their algorithms using either a combination of pharmacy claims and healthcare utilization data (ambulatory medical visits, emergency department visits or hospitalizations) (22, 23, 28, 30-33, 36), or only healthcare utilization data (12, 20, 21, 24-27, 29, 38). Three studies developed algorithms based exclusively on pharmacy claims data (34, 35, 37). Nearly all publications used ICD-9-CM or

ICD-9 codes to identify asthma patients, and consistently used the 493.X (asthma) code (Table 4), although two studies did not provide the specific codes used (22, 38). The majority of studies reported sensitivity, specificity or PPV values, whereas six studies reported all four key diagnostic measures of accuracy (20, 23, 25, 31, 36, 38).

Pediatric populations

Among studies conducted in pediatric populations, PPV ranged from 41 to 92%, NPV from 85 to 99%, sensitivity from 31 to 96%, and specificity from 27 to 99%. Of these, three studies provided evidence that one asthma diagnosis from an ambulatory medical visit over a one-year period was adequate to identify pediatric asthma cases (sensitivity $\geq 85\%$, PPV $\geq 75\%$) (12, 24, 27). In contrast, Lix *et al.*, which used self-reported data as the basis for their reference standard, reported a sensitivity of 30% (23). Additionally, Korzyrskyj *et al.* showed that the accuracy was enhanced when a combination of asthma medications and ambulatory medical visits were considered in the algorithms (sensitivity $\geq 80\%$ and PPV $\geq 90\%$) (22), although the authors did not provide the list of respiratory medications considered. The study by Moth *et al.* (37) developed and validated several algorithms exclusively on pharmacy claims data and the highest sensitivity (63%) and specificity (86%) were reported in the operational definition which included, over a one-year period, at least one respiratory medication, and required inhaled beta2-agonists or inhaled corticosteroids (ICS) to be filled at least twice and excluded SABA in liquid form. Bechtold *et al.* also validated a medication-based algorithm and observed that the sensitivity increased when the time frame used to identify asthma cases was lengthened to four years (34).

Adolescent/Adult populations

Among studies conducted in adult or adolescent populations, PPV ranged from 35 to 100%, NPV from 82 to 100%, sensitivity from 7 to 96%, and specificity from 27 to 99%. Similar to pediatric populations, the validity of these algorithms were reasonably good when at least one ambulatory medical visit, emergency department visit, or hospitalization for asthma was identified over a one-year period (PPV: 70-90%; specificity: 89-100%) (12, 21, 23). However, reported sensitivity values were fairly low. For example, Lix *et al.* (23) and Huzel *et al.* (21) reported sensitivity values ranging between 13 to 60%, although their reference standard consisted of self-reported data. Additionally, Biffi *et al.* (33) reported sensitivity values which ranged between 39 and 64% but the algorithms included only hospitalizations and pharmacy claims data and omitted ambulatory medical encounters. Although authors explained that they selected their algorithms to avoid detecting false disease cases, specificity values were not reported. As exemplified by Lujic *et al.* (36) and Hajibandeh *et al.* (38), specificity values were particularly high when algorithms were constructed using solely hospitalization data (93-100%), at the expense of much lower sensitivity values (7-18%). Of note, Gershon *et al.* (20) showed that the validity was increased when two or more ambulatory medical visits or one hospitalization (or both criteria) were identified over a two-year period (sensitivity: 84%; specificity: 77%). Similarly, Vollmer *et al.* (30) reported that increasing the time frame of asthma outpatient encounters to two years resulted in an enhanced capacity to capture prevalent asthma cases, although they did not report any diagnostic accuracy measure for this operational definition. Another strategy to enhance diagnostic accuracy was suggested by Blais *et al.* (12) who showed that the PPV increased when the diagnosis was made by a pulmonologist. For example, for patients aged between 16-44 years old, the PPV was found to be 75% for pulmonologists and 67% for family physicians when at least one asthma diagnosis was recorded

over a 1-year period. Additionally, Dore *et al.* (29) focused on the identification of prevalent asthma cases and reported a PPV of 74% when at least one asthma diagnosis was identified in the 6-month period prior to initiating a long-acting beta-2 agonist, although the PPV decreased with age. Authors of this study also reported PPVs according to sex, although they did not observe any statistically significant differences.

Discussion

Overall, findings from this review suggest that healthcare administrative data are adequate to capture asthma cases. Several high-quality studies were identified, although significant heterogeneity was observed across studies in terms of patient characteristics, types of reference standards used, and diagnostic accuracy measures reported. Definitions which included at least one diagnosis from health service utilisation data over a one-year period were the most commonly reported algorithms and were generally valid across different age groups. For this review, several strategies that can increase the validity of the algorithms have emerged, including: 1) lengthening the time frame used to capture asthma cases; 2) requiring at least two asthma diagnoses; 3) including diagnoses recorded by a pulmonologist.

A number of valid asthma algorithms have been reported in the literature, suggesting that healthcare administrative databases can provide a vast arena to conduct population-based asthma research. However, prior to embarking in an administrative database study and selecting the best case-finding algorithm, researchers must assess the relative importance of sensitivity, specificity, PPV, and NPV, and prioritize the accuracy measure that is most relevant to the research question (40). As a prime example, it is desirable to select algorithms that have higher sensitivities for surveillance studies, since this approach minimizes the number of missed cases (40, 41). Most studies in this review tested multiple algorithms to identify the one which has the best trade-off

between sensitivity and specificity. Generally, lengthening the time frame to capture asthma cases or increasing the number of diagnoses increased the specificity, at the cost of a lower sensitivity. Operational definitions based solely on hospitalization data were not sensitive, albeit highly specific, since this approach tends to capture more moderate-to-severe asthma patients. On the other hand, a significant number of studies chose the PPV as their main measure of validity, which is important when identifying a cohort defined by disease status. High PPVs and NPVs ensure that only persons who truly have the condition of interest are captured (40), and are desirable in studies seeking to examine causal or association relationships. Studies which used a combination of pharmacy claims data and healthcare utilization data generally had favourable PPV values.

Pharmacy claims data were incorporated in many of the algorithms identified in this review, although many studies conducted in the US and in Canada did not use this approach. A reason for this may be explained by the paucity of databases which comprehensively link all pharmacies to a central data system in these countries. For example, several Canadian databases such as the *Régie de l'assurance de maladie du Québec* only provide prescription medication data for the elderly, recipients of social assistance, and individuals who do not have access to a private drug insurance program through their employer. On the other hand, many US databases only cover commercially insured individuals. Along the same lines, medications dispensed in the hospital setting (emergency department, inpatient wards, same-day surgery clinics) are not always captured in administrative databases. Thus, diagnostic algorithms based on pharmacy claims data may exclude certain segments of the population, which may in turn reduce their generalizability and usefulness for population-based studies, including disease surveillance projects. Additionally, pharmacy claims data typically include prescriptions dispensed in

community pharmacies. Therefore, prescriptions which were written by the physician but not filled by the patient will not be captured. It is also possible that some epidemiologists who conducted these studies did not have access to medication data, which are more commonly used by pharmacoepidemiologists. Although findings from this review suggest that algorithms using pharmacy claims data were generally valid, it is unclear which asthma medications can optimize the diagnostic accuracy. It is also unclear to which extent pharmacy claims data can enhance the capacity to capture asthma cases, since the validity of medication-based algorithms were not drastically different from those which used exclusively diagnostic codes. Moreover, the few studies that evaluated the change in validity of adding medications to healthcare utilization data did not report important changes in the diagnostic accuracy measures (10, 22, 23, 29, 33, 36). Thus, further research is warranted to explore the relevance of incorporating medication data into case-finding asthma algorithms. We hypothesize that pharmacy claims data can be used to efficiently identify asthma patients who have low rates of health services utilization or who appear to have a better level of disease control or a milder form of the disease. Due to the step-care approach to asthma therapy (2), whereby treatments are prescribed or adjusted based on a patient's level of disease severity and control, it may be possible to tailor algorithms to different levels of disease severity, although further studies are required to substantiate this concept.

It was difficult to compare the validity of algorithms between pediatric and adult populations, since only three studies stratified their validity statistics according to different age groups (12, 23, 29). However, the disease progression bias may have affected several pediatric studies, since it has been estimated that less than 50% of children with early-onset wheezing will go on to develop asthma during adolescence (42). Not only it is not possible to routinely assess airflow limitation in this age group, episodic respiratory symptoms such as wheezing and cough

are also common in children without asthma (2). This difficulty in making confident diagnosis of asthma in children 5 years and younger further highlights the necessity to ensure that the time gap between the index and reference test is as small as possible.

Broadly speaking, it is easier to assess the clinical usefulness of algorithms in studies in which authors report disease prevalence, as well as multiple measures of diagnostic accuracy (sensitivity, specificity, and predictive values) for several different algorithms (43), and across various age groups. However, few studies in this review delved into this level of detail due to methodological constraints. Some studies also failed to provide sufficient details on patient selection procedures and choice of reference standards, thus limiting our capacity to comprehensively evaluate their usefulness. Although several studies were methodologically sound, the majority of studies used medical chart review as the reference standard for the asthma diagnosis. However, such an approach is not optimal, as getting a definitive diagnosis of asthma would require pulmonary function tests in addition to symptom assessment – information that is not consistently recorded in medical charts (12). In addition, a recent study by Aaron *et al.* (44) found that a diagnosis of asthma could not be established in 33% of adults with physician-diagnosed asthma, following a medical assessment consisting of home peak flow and symptom monitoring, spirometry, and serial bronchial challenge tests. Hence, absence of an asthma diagnosis in the medical chart does not automatically imply that a patient does not have asthma, and vice-versa. The majority of studies acknowledged this limitation but explained that this methodological choice was made due to feasibility and practical reasons. Yet, when an appropriate reference standard is selected and patients are randomly sampled from the general population, the disease prevalence approximates the population prevalence and provides

unbiased estimates of sensitivity, specificity, PPV, and NPV (43). This approach, though ideal, may not always be feasible in all research settings.

All in all, this review demonstrated that the validity of healthcare administrative data for asthma research is adequate, since misclassification of clinical information appears to be minimal. Because administrative claims data are generated primarily for reimbursement purposes, data on health service use and charges are relatively complete for services covered by the health plan of the database (45). Nevertheless, healthcare delivery system coverage for an individual can change over time; thus, the possibility for extended longitudinal analyses may be compromised. This limitation highlights the necessity to ensure that the time frame to capture asthma cases is not too long—we recommend that it should preferably not exceed two years. Further, the incorporation of EHR data may be beneficial, since they contain a wealth of clinical information, such as reason for medication prescription, laboratory tests results, and patient vitals. However, issues related to data completeness, coupled with their lack of interoperability across health systems, add another layer of complexity for conducting longitudinal studies using EHR data, especially if an individual seeks care from more than one provider (45). In theory, linkage of EHRs and administrative claims may drive the development of better performing asthma case-finding algorithms and merits further investigation; however, such an endeavor may be complex and resource intensive.

The results presented in this review should be interpreted in the light of some limitations. Namely, articles whose full-texts were not available in English or French were excluded, which may have introduced a language bias. There was also a possibility of missing articles that were not indexed in the bibliographic databases under terms related to administrative data or

validation. Nonetheless, our rigorous systematic research methods combined with the grey literature search, ensured that our search strategy was optimized. Furthermore, potential limitations concerning the data extraction procedure remain. Ideally, two reviewers should have each conducted the data extraction independently. Yet in this review, one reviewer extracted the relevant information, whereas a second reviewer validated the extracted information by the first reviewer and disagreements were resolved by consensus or by a third reviewer. This methodological approach, though not optimal, was chosen to ensure the timeliness of data collection. In an effort to maximize the accuracy of collected data, several quality control checks were conducted by a third reviewer. Finally, publication bias cannot be ruled out, whereby asthma diagnostic algorithms with poor validity may have been withheld from publication.

Conclusions

Healthcare administrative databases appear to adequately identify asthma patients. Algorithms that included at least one diagnostic code for asthma or that required a diagnosis by a respiratory physician appeared to be highly valid. Further research is required to confirm if algorithms based on both asthma diagnoses and asthma medications can result in a more enhanced validity. The relevance and choice of a specific algorithm should not be made arbitrarily, but rather be based on the research question and availability of data elements in the administrative database of interest.

Declaration of interest

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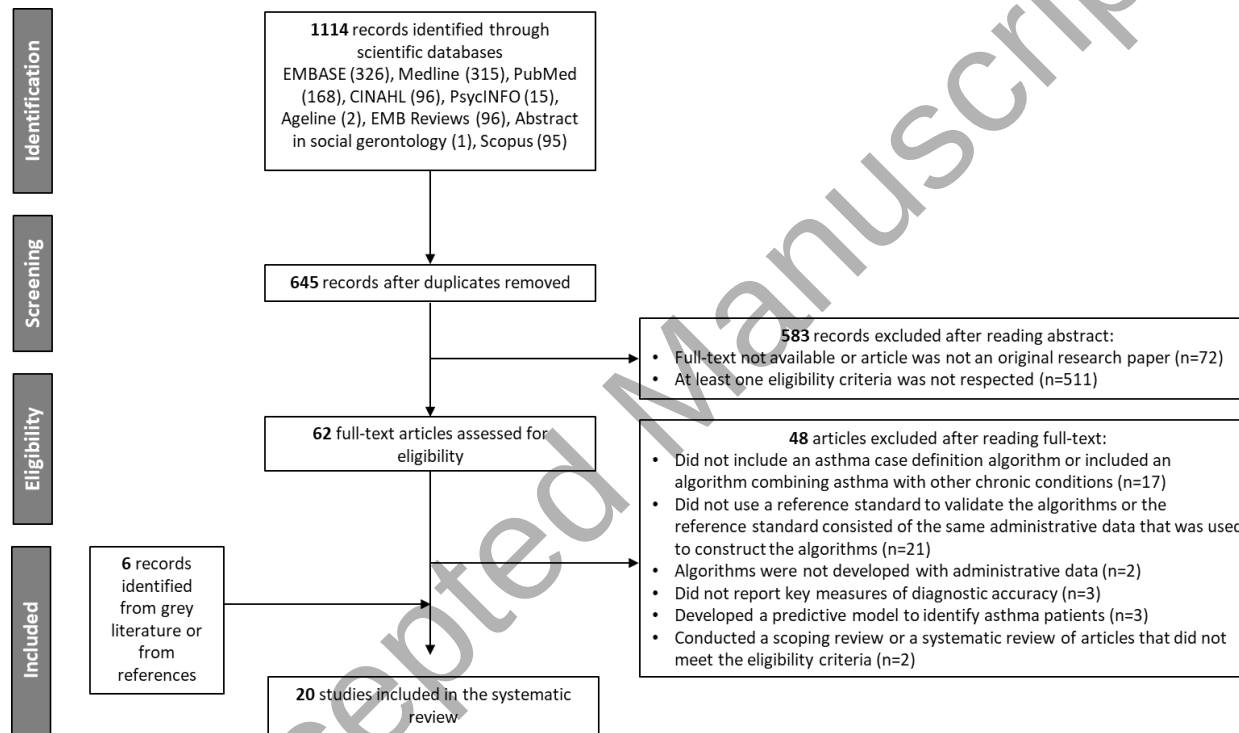


Figure 1. PRISMA-style flow chart of study selection and review

Table 1. Study characteristics (n=20)

Authors, year, Country	Primary validation study?	Sample characteristics (validation sample size), study period	Healthcare Administrative data source	Administrative data type	Reference standard
Andrade <i>et al.</i>, 2013 (32) United States	No	Women delivering a live born infant (n=133) 2001-2007	The Medication Exposure in Pregnancy Risk Evaluation Program database	Ambulatory medical visits ED visits Hospitalizations Pharmacy claims	Chart review
Bechtold <i>et al.</i>, 2012 (34) Italy	Yes	Pediatric/adolescent population 6-7 y (n=7,014) 13 y (n=3,232) 2000-2003	Italian Public Health Service Database	Pharmacy claims	Self-report (parent)
Biffi <i>et al.</i>, 2017 (33) Italy	No	Pediatric and adult populations 0-39 y (validation <i>n</i> unclear) 2010	Lombardy Healthcare Utilization databases	Hospitalizations Pharmacy claims	Chart review
Bianchi <i>et al.</i>, 2011 (35) Italy	Yes	Pediatric/adolescent population 6-17 y (n=244) 2008	Lombardy National Health Service database	Pharmacy claims	Chart review
Blais <i>et al.</i>, 2006 (12) Canada	Yes	Adolescent and adult populations 16-44 y (n=359) 45-80 y (n=367)	<i>Régie de l'assurance maladie du Québec</i> (Medical Services database)	Ambulatory medical visits	Chart review

Authors, year, Country	Primary validation study?	Sample characteristics (validation sample size), study period	Healthcare Administrative data source	Administrative data type	Reference standard
		2000-2002			
Bronstein <i>et al.</i>, 2000 (27) United States	Yes	Pediatric/adolescent population 2-13 y (n=98) 1994-1995	Medicaid claims database	Ambulatory medical visits Medical procedures	Chart review
Dombkowski <i>et al.</i> 2012 (28) United States	Yes	Pediatric/adolescent population 2-18 y (n=440) 2005-2006	Medicaid database and Children's Special Health Care Services database	ED visits Ambulatory medical visits Hospitalizations Pharmacy claims Medical procedures	Self-report (parent)
Dore <i>et al.</i>, 2014 (29) United States	No	Adult population ≥20 y, LABA and LABA/ICS initiators or switchers (n=370) 2005-2008	Normative Health Information Database, a claims database of a large US commercial health plan (UnitedHealth Care).	Ambulatory medical visits Hospitalizations	Chart review
Gershon <i>et al.</i>, 2009 (20) Canada	Yes	Adult population 19-80 y (n=518) 2003	Ontario Health Insurance Plan database	Ambulatory medical visits Hospitalizations	Chart review
Hajibandeh <i>et al.</i>, 2017 (38) United Kingdom	No	Adult population > 18 y who underwent any types of colectomy (n=267)	Hospital Episodes Statistics (HES)	Hospitalizations	Chart review

Authors, year, Country	Primary validation study?	Sample characteristics (validation sample size), study period	Healthcare Administrative data source	Administrative data type	Reference standard
		2015-2016			
Huzel <i>et al.</i>, 2002 (21) Canada	Yes	Adult population 20-44 y (n=2,479) 1993-1994	The Manitoba Population Health Research Repository	Ambulatory medical visits	Self-report
Kozyrskyj <i>et al.</i> (2009)(22) Canada	No	Pediatric population 7-8 y (n=723) 2002-2005	Manitoba's Healthcare databases	Ambulatory medical visits Hospitalizations Pharmacy claims	Clinical test
Lix <i>et al.</i>, 2006 (23) Canada	No	Adolescent/adult populations 12-18 y (n=833) ≥19 y (n=5,589) 2000-2001	Population Health Research Data Repository housed at the Manitoba Centre for Health Policy	Ambulatory medical visits Hospitalizations Pharmacy claims	Self-report
Lujic <i>et al.</i>, 2017 (36) Australia	No	Adult population with multimorbidity ≥45 y (n= 11,384) 2007-2009	-New South Wales admitted patient data collection -Pharmaceutical Benefits Scheme	Hospitalizations Pharmacy claims	Self-report
Moth <i>et al.</i>, 2007 (37) Denmark	Yes	Pediatric population 6-14 y (n=6,352) 2000-2003	The regional Health Service Register and the Odense Pharmacoepidemiologic Database	Pharmacy claims	Chart review
Omand <i>et al.</i>, 2019 (25)	Yes	Pediatric population	Canadian Institute for Health Information, Discharge Abstract	Ambulatory medical visits	Self-report

Authors, year, Country	Primary validation study?	Sample characteristics (validation sample size), study period	Healthcare Administrative data source	Administrative data type	Reference standard
Canada		1-5 y (n=3,642) 2008-2013	Database, Ontario Health Insurance Plan	Hospitalizations	(parent)
To et al., 2006 (24) Canada	Yes	Pediatric/adolescent populations 0-18 y (n=630) 2000-2001	Ontario Health Insurance Plan database	Ambulatory medical visits	Chart review
Vollmer et al., 2004 (30) United States	Yes	Adolescent/adult populations 15-55 y (n=132) 1999	Kaiser Permanente Northwest Division databases	ED visits Ambulatory medical visits Hospitalizations Pharmacy claims	Chart review
Wakefield et al., 2006 (31) United States	Yes	Pediatric population 6 months-18 y Medicaid:1998-2001 (n=3,905) ConnectiCare: 2001-2004 (n=1,458)	Medicaid and ConnectiCare databases	ED visits Ambulatory medical visits Hospitalizations Pharmacy claims	Self-report (parent)
Wilchesky et al., 2004 (26) Canada	No	Geriatric population ≥66 y (n= 1,099) 1995-1996	<i>Régie de l'assurance maladie du Québec</i> (Medical Services database)	Ambulatory medical visits	Chart review

Abbreviations: ED: Emergency department; ICS: Inhaled corticosteroids; LABA: Long-acting beta2-agonists; n: number, y: years old.

Table 2. Chart review or clinical test as reference-standard (n=13)

Author, year	Algorithm case definitions*	Se (95% CI)**	Sp (95% CI)**	PPV (95% CI)**	NPV (95% CI)**
Andrade et al., 2013 (32)	(≥2 ambulatory medical visits at least 30 days apart) OR (≥1 hospitalization) OR (≥1 ambulatory medical visit and ≥1 pharmacy claim) over 1 year prior to pregnancy through the date of delivery. Medications: SABA, LABA, ICS, LTRA, mast cell stabilizer, methylxanthine	-	-	95 (91-99)	-
Biffi et al., 2017 (33)	<40 y and ≥1 of the following criteria, over 1 year: Benefitted of exemption for asthma; ≥1 hospitalization; ≥2 pharmacy claims of any of the following drugs: LTRA, chromones; ≥2 pharmacy claims of any of the following drugs: SABA, LABA/ICS fixed combinations (only 0-19 y); ≥2 pharmacy claims of ICS AND ≥1 pharmacy claim of SABA; ≥2 pharmacy claims of ICS in addition to ≥2 pharmacy claims of ipratropium, oxitropium or theophylline (only 0-19 y); ≥1 pharmacy claim of antibiotics (ATC: J01; only 20-39 y); AND ≥1 of the following criteria: ≥2 pharmacy claims of theophylline and ≥2 pharmacy claims of any of the following drugs: beta-agonist, ipratropium, oxitropium, ICS; ≥2 pharmacy claims of SABA or LABA/ICS fixed combinations; ≥2 pharmacy claims of ICS AND ≥2 pharmacy claims of ipratropium or oxitropium	39 (-)	-	-	-
	<40 y and ≥1 of the following criteria, over 1 year: ≥1 pharmacy claim of one of the following drugs: SABA, LABA, LABA/ICS, ICS, chromones, LAAC, theophylline; ≥1 pharmacy claim of LTRA and ≥1 pharmacy claim of any other respiratory drug; ≥1 pharmacy claim of OCS and ≥1 pharmacy claim for any respiratory drug	63 (-)	-	-	-
	<40 y and ≥1 of the following criteria, over 1 year: ≥2 pharmacy claims of one of the following drugs: SABA, LABA, LABA/ICS, ICS, chromones, LAAC, theophylline; ≥2 pharmacy claims of LTRA and ≥2 pharmacy claims of any other drug for chronic respiratory diseases; ≥2 pharmacy claims of OCS and ≥2 pharmacy claims of any other respiratory drug	31 (-)	-	-	-
	6-17 y, ≥1 pharmacy claim of one of the following drugs: SABA, non-SABA, or OCS over 1 year	90 (-)	98 (-)	32 (-)	10 (-)
Blais et al., 2006 (12)	≥1 ambulatory medical visit over 1 year: 16-44 y, seen by a family physician 16-44 y, seen by a pulmonologist 45-80 y, seen by a family physician 45-80 y, seen by a pulmonologist	- 97 (94-100) - 94 (92-96)	- 85 (78-94) - 65 (56-75)	67 (58-75) 75 (68-85) 60 (50-70) 78 (69-87)	99 (97-100) 96 (92-100) 100 (96-100) 93 (87-98)
	≥2 ambulatory medical visits over 1 year: 16-44 y, seen by a family physician 16-44 y, seen by a pulmonologist 45-80 y, seen by a family physician 45-80 y, seen by a pulmonologist	- 87 (80-94) - 84 (77-91)	- 94 (89-99) - 83 (75-90)	78 (65-90) 77 (64-90) 68 (56-80) 87 (78-96)	- - - -
	2-13 y, ≥1 ambulatory medical visit over 1 year 2-13 y, ≥1 medical procedure corresponding to a nebulizer treatment over 1 year	-	-	88 (-) 88 (-)	85 (-) 97 (-)
	≥1 hospitalization or ≥1 ambulatory medical visit, 6 months before initiating a LABA: All population	-	-	74 (63-82)	-

Author, year	Algorithm case definitions*	Se (95% CI)**	Sp (95% CI)**	PPV (95% CI)**	NPV (95% CI)**
	20-39 y	-	-	79 (58-93)	-
	40-64 y	-	-	73 (60-83)	-
	≥65 y	-	-	60 (15-95)	-
	Men only	-	-	74 (56-87)	-
	Women only	-	-	74 (60-85)	-
Gershon <i>et al.</i>, 2009 (20)	19-80 y, ≥1 ambulatory medical visit OR ≥1 hospitalization over unspecified period (or both criteria): Against expert panel dx Against practitioner chart dx	95 (90-98) 92 (88-96)	59 (54-64) 64 (58-68)	51 (45-57) 61 (55-66)	96 (93-98) 93 (89-96)
	19-80 y, ≥2 ambulatory medical visits OR ≥1 hospitalization over 2 years (or both criteria): Against expert panel dx Against practitioner chart dx	84 (77-89) 81 (74-86)	77 (72-81) 82 (77-86)	62 (54-68) 73 (66-78)	91 (88-94) 87 (83-91)
	19-80 y, ≥2 ambulatory medical visits OR ≥1 hospitalization over 3 years (or both criteria): Against expert panel dx Against practitioner chart dx	85 (79-90) 82 (76-87)	75 (70-79) 79 (75-84)	60 (54-67) 71 (65-77)	92 (88-95) 88 (83-91)
	19-80 y, ≥3 ambulatory medical visits OR ≥1 hospitalization over 2 years (or both criteria): Ref. standard: expert panel dx Ref. standard: practitioner chart dx	74 (67-81) 68 (61-74)	87 (83-90) 90 (86-93)	72 (64-78) 80 (73-86)	88 (85-92) 82 (78-86)
	19-80 y ≥3 ambulatory medical visits OR ≥1 hospitalization over 3 years (or both criteria): Ref. standard: expert panel dx Ref. standard: practitioner chart dx	76 (68-82) 70 (64-77)	85 (81-88) 88 (84-92)	69 (61-76) 78 (72-84)	89 (85-92) 83 (79-87)
	>18 y, ≥1 hospitalization over unspecified period	18 (-)	100 (-)	100 (-)	81 (-)
Kozyrskyj <i>et al.</i>, 2009 (22)	7-8 y, ≥1 hospitalization OR ≥2 ambulatory medical visits OR ≥4 pharmacy claims over 1 year	47 (35-60)	92 (78-98)	91 (76-98)	-
	7-8 y, ≥1 hospitalization OR ≥2 ambulatory medical visits OR ≥2 pharmacy claims over 1 year	67 (54-78)	92 (78-98)	94 (82-99)	-
	7-8 y, ≥1 hospitalization OR ≥1 ambulatory medical visit OR 2 pharmacy claims over 1 year	77 (65-78)	92 (78-98)	94 (82-99)	-
	7-8 y, ≥1 hospitalization OR ≥1 ambulatory medical visit OR ≥2 bronchodilators OR ≥1 controller medication over 1 year	80 (69-89)	89 (74-97)	93 (83-98)	-
	7-8 y, ≥1 hospitalization OR ≥1 ambulatory medical visit OR ≥2 bronchodilators OR (≥1 bronchodilator and ketotifen or oral steroid) OR ≥1 controller medication over 1 year	82 (70-90)	83 (67-94)	90 (79-96)	-
Moth <i>et al.</i>, 2007(37)	6-14 y, ≥1 pharmacy claim, excluding beta2-agonists in liquid form, over 1 year	96 (95-96)	43 (41-45)	-	-
	6-14 y, ≥1 pharmacy claim, excluding beta2-agonists in liquid form or if an inhaled beta2-agonist was filled only once, over 1 year	83 (81-84)	73 (71-75)	-	-
	6-14 y, ≥1 pharmacy claim, excluding beta2-agonists in liquid form or if an inhaled beta2-agonist or ICS was filled only once, over 1 year	63 (62-65)	86 (84-87)	-	-
	6-14 y, ≥1 pharmacy claim, excluding beta2-agonists in liquid form or if an inhaled beta2-agonist or an ICS was filled only once, over a 6-month capture period and a 1-year observation window [†]	78 (76-79)	81 (79-83)	-	-
	6-14 y, ≥1 pharmacy claim, excluding beta2-agonists in liquid form or if an inhaled beta2-agonist or an ICS was filled only once, over a 1-year capture period and a 6-month observation window [†]	59 (58-60)	87 (85-88)	-	-
	6-14 y, ≥1 pharmacy claim, excluding beta2-agonists in liquid form or if an inhaled beta2-agonist or an ICS was filled only once, over a 9-month capture period and observation window [†]	70 (69-71)	83 (81-85)	-	-
To <i>et al.</i>, 2006 (24)	0-18 y, 1 ambulatory medical visit	91 (-)	83 (-)	-	-

Author, year	Algorithm case definitions*		Se (95% CI)**	Sp (95% CI)**	PPV (95% CI)**	NPV (95% CI)**
Vollmer et al., 2004 (30)	<i>Medication dispensing criteria</i>	15-55 y, (≥ 2 ambulatory medical visits) OR (1 ambulatory medical visit and ≥ 2 ED visit or hospitalizations) OR (any industrial medicine visit) OR (any visit and either one of two medication dispensing criteria) in the past year	-	-	95 (-)	-
	1) (≥ 1 dispensing of either an ICS or of cromolyn AND ≥ 1 dispensing of beta-agonist inhaler); 2) ≥ 4 dispensings of beta-agonist inhalers; 3) ≥ 1 order for nebulizer treatment in the outpatient setting.	15-55 y, 1 ambulatory medical visit in the past year	-	-	90 (-)	-
		15-55 y, ≥ 4 beta-agonists with or without a nebulizer treatment order, but no asthma visits and no ICS in the past year	-	-	70 (-)	-
		15-55 y, 1 ED visit for asthma and nebulizer treatment order, but no other asthma medication dispensing criteria met and no other types of asthma visits in the past year	-	-	100 (-)	-
		15-55 y, 1 hospitalization, but neither medication dispensing criterion met and no ambulatory visits of any kind in the past year	-	-	50 (-)	-
		15-55 y, 1 ED visit or urgent care visit, but no other types of asthma visits and no medication dispensing criteria met in the past year	-	-	80 (-)	-
		15-55 y, 1 nebulizer treatment but no asthma visits of any kind and no other medication dispensing criteria in the past year	-	-	27 (-)	-
Wilchesky et al., 2004 (26)	≥ 66 y, 1 ambulatory medical visit in the year prior the start of the MOXXI study: Ref. standard: dx recorded by MOXXI physicians only (primary care physicians) Ref standard: dx recorded by all billing physicians		30 (27-33) 43 (40-46)	99 (99-99) 97 (97-97)	- -	- -

Abbreviations: ED: Emergency department; ICS: Inhaled corticosteroids; LAAC: Long-acting anticholinergics; LABA: Long-acting beta2-agonists; LTRA: Leukotriene receptor antagonists; SABA: Short-acting beta2-agonists; y: years old.

*Ambulatory medical visits, ED visits and hospitalizations refer to medical encounters that have an asthma diagnosis.

**When applicable, validity statistics were rounded to the nearest integer.

†Capture period: period in which children were identified by their first prescription of anti-asthmatic medication succeeded by an observation period in which the children's subsequent prescriptions were registered.

Table 3. Self-report as reference standard (n=7)

Author, year	Algorithm case definitions	Se (95% CI)*	Sp (95% CI)*	PPV (95% CI)*	NPV (95% CI)*
Bechtold <i>et al.</i>, 2012 (34)	≥1 pharmacy claim of an inhaled bronchodilator (LABA, SABA) over 1 year:				
	Ref. standard: wheezing symptoms in past year; Age groups 6-7 y & 13 y	32 (31-33)	98 (98-98)	-	-
	Ref. standard: wheezing symptoms in past year; Age group 6-7 y	34 (32-35)	98 (97-98)	-	-
	Ref. standard: wheezing symptoms in past year; Age group 13 y	28 (26-29)	99 (98-99)	-	-
	≥1 pharmacy claim of an inhaled bronchodilator (LABA, SABA) over 2 years:				
	Ref. standard: wheezing symptoms in past year; Age groups 6-7 y & 13 y	56 (54-56)	94 (93-94)	-	-
	Ref. standard: wheezing symptoms in past year; Age group 6-7 y	61 (60-62)	92 (92-93)	-	-
	Ref. standard: wheezing symptoms in past year; Age group 13 y	44 (42-45)	97 (96-97)	-	-
	≥1 pharmacy claim of an inhaled bronchodilator (LABA, SABA) over 4 years:				
	Ref. standard: wheezing symptoms in past year; Age groups 6-7 y & 13 y	70 (69-71)	83 (83-84)	-	-
	Ref. standard: wheezing symptoms in past year; Age group 6-7 y	76 (75-77)	79 (78-80)	-	-
	Ref. standard: wheezing symptoms in past year; Age group 13 y	57 (56-59)	93 (92-94)	-	-
	≥1 pharmacy claim of an inhaled bronchodilator (LABA, SABA) over 4 years:				
	Ref. standard: physician diagnosis of asthma; Age groups 6-7 y & 13 y	61 (60-62)	84 (84-85)	-	-
Dombkowski <i>et al.</i>, 2012 (28)	Ref. standard: physician diagnosis of asthma; Age group 6-7 y	68 (67-69)	80 (79-81)	-	-
	Ref. standard: physician diagnosis of asthma Age group 13 y	50 (48-51)	94 (94-95)	-	-
	Children with asthma dx (2-18 y):	-	-	89 (-)	-
	≥1 pharmacy claim AND ≥1 any other combination of health services utilization over 2 years	-	-	93 (-)	-
	≥6 SABA/year AND ≥1 any other combination of health services health utilization over 2 years	-	-	100 (-)	-
	≥1 hospitalization OR ≥1 ED visit AND ≥1 any other combination of services utilization over 2 years	-	-	73 (-)	-
	≥1 hospitalization OR ≥1 ED visit for asthma only over 2 years	-	-	65 (-)	-
	≥1 ambulatory medical visit AND ≥1 any other combination of services utilization over 2 years	-	-	69 (-)	-
	≥1 ambulatory medical visit over 2 years	-	-	71 (-)	-
	≥1 procedure or durable medical equipment claim AND ≥1 any other combination of health services utilization over 2 years	-	-	67 (-)	-
Huzel <i>et al.</i>, 2002 (21)	≥1 procedure or durable medical equipment claim over 2 years	-	-	-	-
	20-44 y, ≥1 ambulatory medical visit over 1 year before the survey:				
	Ref. standard: Asthma attack	38 (-)	98 (-)	-	-
	Ref. standard: Asthma medication	41 (-)	99 (-)	-	-
	Ref. standard: Attack or medication	38 (-)	99 (-)	-	-
	Ref. standard: Attack and medication	43 (-)	98 (-)	-	-
	Ref. standard: Attack, medication or symptoms	8 (-)	100 (-)	-	-
	20-44 y, ≥1 ambulatory medical visit over 2 years before the survey:				
	Ref. standard: Asthma attack	51 (-)	98 (-)	-	-
	Ref. standard: Asthma medication	54 (-)	98 (-)	-	-

Author, year	Algorithm case definitions	Se (95% CI)*	Sp (95% CI)*	PPV (95% CI)*	NPV (95% CI)*
	Ref. standard: Attack or medication	50 (-)	99 (-)	-	-
	Ref. standard: Attack and medication	57 (-)	98 (-)	-	-
	Ref. standard: Attack, medication or symptoms	10 (-)	100 (-)	-	-
	20-44 y, ≥1 ambulatory medical visit over 5 years before the survey:				
	Ref. standard: Asthma attack	63 (-)	97 (-)	-	-
	Ref. standard: Asthma medication	65 (-)	97 (-)	-	-
	Ref. standard: Attack or medication	61 (-)	98 (-)	-	-
	Ref. standard: Attack and medication	70 (-)	96 (-)	-	-
	Ref. standard: Attack, medication or symptoms	14 (-)	99 (-)	-	-
Lix et al., 2006 (23)	≥1 ambulatory medical visit over 1 year:				
	≥12 y	31 (27-35)	99 (99-99)	70 (64-76)	94 (94-95)
	12-18 y	30 (21-38)	98 (97-99)	70 (57-83)	90 (88-92)
	19-49 y	30 (24-36)	99 (99-99)	72 (63-81)	95 (94-95)
	≥50 y	33 (26-39)	99 (98-99)	69 (59-79)	95 (94-96)
	≥2 ambulatory medical visits over 1 year:				
	≥12 y	18 (15-21)	100 (99-100)	77 (70-85)	93 (93-94)
	12-18 y	16 (9-23)	99 (99-100)	82 (66-98)	89 (86-91)
	19-49 y	17 (12-22)	100 (99-100)	74 (62-86)	94 (93-95)
	≥50 y	21 (15-26)	100 (99-100)	80 (68-91)	94 (93-95)
	≥1 pharmacy claim over 1 year:				
	≥12+ y	55 (51-60)	96 (95-96)	55 (50-59)	96 (96-97)
	12-18 y	43 (34-53)	97 (96-98)	71 (60-81)	92 (90-94)
	19-49 y	50 (44-57)	98 (97-98)	62 (55-69)	96 (95-97)
	≥50 y	69 (62-76)	94 (93-95)	46 (40-52)	97 (97-98)
	≥1 hospitalization OR ≥1 ambulatory medical visit over 1 year:				
	≥12 y	31 (27-35)	99 (99-99)	70 (65-76)	94 (94-95)
	12-18 y	30 (21-38)	98 (97-99)	70 (57-83)	90 (88-92)
	19-49 y	30 (24-36)	99 (99-99)	72 (63-81)	95 (94-95)
	≥50 y	34 (27-40)	99 (98-99)	69 (59-78)	95 (94-96)
	≥1 hospitalization OR ≥2 ambulatory medical visits over 1 year:				
	≥12 y	19 (16-22)	100 (99-100)	78 (70-85)	93 (93-94)
	12-18 y	16 (9-23)	99 (99-100)	82 (66-98)	89 (86-91)
	19-49 y	18 (13-23)	100 (99-100)	75 (63-86)	94 (93-95)
	≥50 y	22 (16-27)	100 (99-100)	79 (68-90)	94 (93-95)
	≥1 hospitalization OR ≥1 ambulatory medical visit OR ≥1 pharmacy claim over 1 year:				
	≥12 y	58 (54-63)	96 (95-96)	54 (50-58)	96 (96-97)
	12-18 y	49 (39-58)	97 (96-98)	70 (60-80)	93 (91-94)
	19-49 y	54 (47-60)	97 (97-98)	60 (53-67)	96 (96-97)
	≥50 y	70 (64-77)	93 (92-94)	45 (39-51)	98 (97-98)
	≥1 hospitalization OR ≥2 ambulatory medical visits OR ≥2 pharmacy claims over 1 year:				

Author, year	Algorithm case definitions	Se (95% CI)*	Sp (95% CI)*	PPV (95% CI)*	NPV (95% CI)*
	≥12 y	47 (43-51)	98 (97-98)	64 (60-69)	95 (95-96)
	12-18 y	33 (25-42)	99 (98-100)	79 (67-90)	91 (89-93)
	19-49 y	42 (35-48)	99 (99-99)	78 (71-85)	95 (95-96)
	≥50 y	61 (54-68)	96 (95-97)	54 (47-60)	97 (96-98)
	≥1 ambulatory medical visit over 2 years:				
	≥12 y	44 (40-48)	98 (98-98)	66 (61-71)	95 (95-96)
	12-18 y	46 (37-55)	97 (95-98)	67 (57-78)	92 (90-94)
	19-49 y	43 (36-49)	99 (98-99)	69 (62-77)	95 (95-96)
	≥50 y	44 (37-51)	98 (97-98)	62 (54-70)	96 (95-97)
	≥2 ambulatory medical visits over 2 years:				
	≥12 y	30 (26-34)	99 (99-99)	74 (68-80)	94 (93-95)
	12-18 y	33 (25-42)	99 (98-100)	84 (73-95)	91 (89-93)
	19-49 y	29 (23-35)	99 (99-100)	73 (64-83)	94 (94-95)
	≥50 y	30 (23-36)	99 (99-99)	70 (60-80)	95 (94-96)
	≥1 pharmacy claim over 2 years:				
	≥12 y	70 (66-74)	94 (93-94)	50 (46-54)	97 (97-98)
	12-18 y	68 (59-76)	95 (94-97)	69 (61-78)	95 (94-97)
	19-49 y	65 (59-72)	96 (95-97)	56 (50-62)	97 (97-98)
	≥50 y	76 (70-82)	91 (90-92)	40 (35-45)	98 (97-99)
	≥1 hospitalization OR ≥1 ambulatory medical visit over 2 years:				
	≥12 y	45 (41-49)	98 (98-98)	66 (61-71)	95 (95-96)
	12-18 y	46 (37-55)	97 (95-98)	67 (57-78)	92 (90-94)
	19-49 y	43 (37-49)	98 (98-99)	69 (61-77)	96 (95-96)
	≥50 y	46 (39-53)	98 (97-98)	63 (55-71)	96 (95-97)
	≥1 hospitalization OR ≥2 ambulatory medical visits over 2 years:				
	≥12 y	31 (27-35)	99 (99-99)	74 (69-80)	94 (94-95)
	12-18 y	33 (25-42)	99 (98-100)	84 (73-95)	91 (89-93)
	19-49 y	30 (24-36)	99 (99-100)	73 (64-82)	95 (94-95)
	≥50 y	32 (25-38)	99 (99-99)	71 (61-80)	95 (94-96)
	≥1 hospitalization OR ≥1 ambulatory medical visit OR ≥1 pharmacy claim over 2 years:				
	≥12 y	73 (69-76)	93 (92-94)	48 (45-52)	97 (97-98)
	12-18 y	69 (61-78)	95 (93-96)	66 (57-74)	95 (94-97)
	19-49 y	70 (64-76)	95 (94-96)	54 (48-59)	98 (97-98)
	≥50 y	77 (71-83)	90 (89-92)	39 (33-44)	98 (98-99)
	≥1 hospitalization OR ≥2 ambulatory medical visits OR ≥2 pharmacy claims over 2 years:				
	≥12 y	58 (53-62)	97 (96-97)	61 (57-65)	96 (96-97)
	12-18 y	49 (39-58)	98 (97-99)	81 (71-90)	93 (91-94)
	≥19-49 y	54 (47-60)	98 (98-99)	73 (66-79)	96 (96-97)
	≥50 y	67 (61-74)	94 (93-95)	48 (42-54)	97 (97-98)
	≥1 ambulatory medical visit over 3 years:				

Author, year	Algorithm case definitions	Se (95% CI)*	Sp (95% CI)*	PPV (95% CI)*	NPV (95% CI)*
	≥12 y	53 (49-57)	97 (97-97)	61 (56-65)	96 (95-96)
	12-18 y	62 (53-71)	95 (94-97)	66 (57-75)	94 (93-96)
	19-49 y	49 (42-55)	98 (97-98)	62 (55-69)	96 (95-97)
	≥50 y	53 (46-60)	97 (96-97)	56 (49-64)	96 (96-97)
	≥2 ambulatory medical visits over 3 years:				
	≥12y	38 (34-42)	99 (98-99)	71 (66-77)	95 (94-95)
	12-18 y	48 (39-57)	98 (97-99)	82 (72-91)	93 (91-94)
	19-49 y	34 (28-40)	99 (99-99)	71 (62-79)	95 (94-96)
	≥50 y	36 (29-43)	99 (98-99)	65 (56-74)	95 (94-96)
	≥1 pharmacy claim over 3 years:				
	≥12 y	75 (71-78)	92 (92-93)	47 (43-50)	98 (97-98)
	12-18 y	77 (69-85)	94 (92-96)	66 (58-74)	96 (95-98)
	19-49 y	70 (64-76)	94 (94-95)	51 (45-56)	98 (97-98)
	≥50 y	79 (73-85)	89 (88-91)	37 (32-42)	98 (98-99)
	≥1 hospitalization OR ≥1 ambulatory medical visit over 3 years:				
	≥12 y	54 (49-58)	97 (96-97)	61 (56-65)	96 (95-96)
	12-18 y	62 (53-71)	95 (94-97)	66 (57-75)	94 (93-96)
	19-49 y	49 (43-56)	98 (97-98)	62 (55-69)	96 (95-97)
	≥50 y	54 (47-61)	97 (96-97)	57 (49-64)	96 (96-97)
	≥1 hospitalization OR ≥2 ambulatory medical visits over 3 years:				
	≥12 y	38 (34-43)	99 (98-99)	71 (66-76)	95 (94-95)
	12-18 y	48 (39-57)	98 (97-99)	82 (72-91)	92 (91-94)
	19-49 y	35 (29-41)	99 (98-99)	71 (62-79)	95 (94-96)
	≥50 y	37 (31-44)	98 (98-99)	65 (56-74)	95 (94-96)
	≥1 hospitalization OR ≥1 ambulatory medical visit OR ≥1 pharmacy claim over 3 years:				
	≥12 y	78 (74-81)	91 (91-92)	44 (41-47)	98 (98-98)
	12-18 y	78 (71-86)	92 (90-94)	61 (53-69)	97 (95-98)
	19-49 y	75 (69-80)	93 (92-94)	48 (43-53)	98 (97-98)
	≥50 y	81 (76-87)	88 (87-90)	36 (31-40)	98 (98-99)
	≥1 hospitalization OR ≥2 ambulatory medical visits OR ≥2 pharmacy claims over 3 years:				
	≥12 y	66 (62-70)	96 (95-96)	58 (54-62)	97 (97-97)
	12-18 y	69 (61-78)	97 (96-98)	77 (69-85)	95 (94-97)
	19-49 y	60 (54-66)	98 (97-98)	68 (61-74)	97 (96-97)
	≥50 y	72 (65-78)	93 (92-94)	45 (39-51)	98 (97-98)
	≥1 ambulatory medical visit over 5 years:				
	≥12 y	64 (59-68)	95 (95-96)	55 (51-59)	97 (96-97)
	12-18 y	75 (67-83)	92 (90-94)	59 (51-67)	96 (95-97)
	19-49 y	61 (54-67)	96 (95-97)	55 (49-61)	97 (96-97)
	≥50 y	61 (54-68)	96 (95-97)	53 (46-59)	97 (96-98)
	≥2 ambulatory medical visits over 5 years:				

Author, year	Algorithm case definitions	Se (95% CI)*	Sp (95% CI)*	PPV (95% CI)*	NPV (95% CI)*	
	≥12 y	50 (46-55)	98 (97-98)	66 (62-71)	96 (95-96)	
	12-18 y	60 (51-70)	97 (95-98)	74 (65-83)	94 (92-96)	
	19-49 y	50 (44-57)	98 (97-98)	65 (58-72)	96 (95-97)	
	≥50 y	44 (37-51)	98 (97-99)	63 (55-71)	96 (95-97)	
	≥1 pharmacy claim over 5 years:					
	≥12 y	82 (78-84)	90 (89-91)	43 (40-46)	98 (98-99)	
	12-18 y	87 (80-93)	91 (89-93)	59 (51-66)	98 (97-99)	
	19-49 y	78 (73-83)	92 (91-93)	45 (40-50)	98 (98-99)	
	≥50 y	83 (77-88)	88 (86-89)	35 (30-39)	98 (98-99)	
	≥1 hospitalization OR ≥1 ambulatory medical visit over 5 years:					
	≥12 y	64 (60-68)	95 (95-96)	55 (51-59)	97 (96-97)	
	12-18 y	75 (67-83)	92 (90-94)	59 (51-67)	96 (95-97)	
	19-49 y	61 (54-67)	96 (95-97)	55 (48-61)	97 (96-97)	
	≥50 y	61 (54-68)	96 (95-97)	53 (46-59)	97 (96-98)	
	≥1 hospitalization OR ≥2 ambulatory medical visits over 5 years:					
	≥12 y	51 (46-55)	98 (97-98)	66 (61-70)	96 (95-96)	
	12-18 y	60 (51-70)	97 (95-98)	74 (65-83)	94 (92-96)	
	19-49 y	50 (44-57)	98 (97-98)	65 (58-72)	96 (95-97)	
	≥50 y	45 (38-52)	98 (97-98)	62 (54-70)	96 (95-97)	
	≥1 hospitalization OR ≥ ambulatory medical visit OR ≥1 pharmacy claim over 5 years:					
	≥12 y	84 (81-87)	89 (88-89)	40 (37-43)	98 (98-99)	
	12-18 y	87 (81-94)	89 (86-91)	54 (47-61)	98 (97-99)	
	19-49 y	82 (77-87)	91 (89-92)	41 (37-46)	98 (98-99)	
	≥50 y	85 (80-90)	86 (85-88)	33 (29-38)	99 (98-99)	
	≥1 hospitalization OR ≥2 ambulatory medical visits OR ≥2 pharmacy claims over 5 years:					
	≥12 y	75 (72-79)	94 (94-95)	54 (50-57)	98 (97-98)	
	12-18 y	80 (73-88)	95 (93-96)	70 (62-78)	97 (96-98)	
	19-49 y	71 (65-77)	96 (95-97)	59 (53-55)	98 (97-98)	
	≥50 y	78 (72-84)	92 (91-93)	43 (38-49)	98 (98-99)	
Lujic et al., 2017 (36)	≥45 y, ≥1 hospitalization over 2 years	7 (6-8)	100 (100-100)	81 (77-84)	87 (87- 87)	
	≥45 y, ≥2 pharmacy claims over 2 years	65 (65-66)	93 (93-93)	57 (57-58)	95 (95-95)	
	≥45 y, ≥1 hospitalization over 2 years OR ≥2 pharmacy claims over 2 years	66 (65-67)	93 (93-93)	57 (57-58)	95 (95-95)	
Omand et al., 2019 (25)	≥1 hospitalization for asthma OR ≥ two separate ambulatory or ED visits over 2 years:					
	1-5 y	81 (75-86)	90 (89-91)	34 (30-38)	99 (98-99)	
	1-3 y	68 (49-83)	91 (89-92)	16 (10-23)	99 (98-100)	
	3-5 y	83 (77-88)	89 (88-90)	41 (36-46)	98 (98-99)	
Wakefield et al., 2006 (31)	Probable asthma [†] : 6 months-18 y	≥1 hospitalization with a primary discharge dx OR ≥1 ED visit OR ≥1 ambulatory medical visit, over 1 year*: -Medicaid children	61 (59-64)	98 (98-99)	97 (96-98)	74 (72-75)

Author, year	Algorithm case definitions	Se (95% CI)*	Sp (95% CI)*	PPV (95% CI)*	NPV (95% CI)*
Persistent asthma [†] : 6 months-18 y <i>Medications used in all algorithms:</i> Bronchodilators (including theophylline and salmeterol), ICS, OCS, and anti- inflammatory drugs (including LTRA)	(≥1 hospitalization or ≥1 ED visit or ≥1 ambulatory medical visit) OR (≥2 pharmacy claims), over 1 year: -Medicaid children	77 (75-79)	98 (97-98)	97 (96-98)	82 (81-84)
	(≥1 hospitalization or ≥1 ED visit or ≥1 ambulatory medical visit) OR (≥1 pharmacy claim), over 1 year: -Medicaid children -ConnectiCare children	90 (89-92) 80 (-)	95 (94-96) 93 (-)	94 (93-95) 75 (-)	92 (90-93) 95 (-)
	(≥4 pharmacy claims) OR (≥1 hospitalization or ≥1 ED visit) OR (≥4 ambulatory medical visits and ≥2 pharmacy claims), over 1 year: -Medicaid children	44 (41-47)	94 (93-94)	69 (65-73)	85 (84-86)
	(≥4 pharmacy claims) OR (≥1 hospitalization or ≥1 ED visit) OR (≥1 ambulatory medical visit and ≥1 anti-inflammatory drug), over 1 year: -Medicaid children	67 (64-70)	93 (92-94)	75 (72-78)	90 (89-91)
	(≥4 pharmacy claims) OR (≥1 hospitalization or ≥1 ED visit) OR (≥2 anti-inflammatory drugs), over 1 year: -Medicaid children	58 (54-61)	94 (93-95)	74 (71-77)	88 (87-89)
	(≥4 pharmacy claims) OR (≥1 hospitalization or ≥1 ED visit) OR (≥1 ambulatory medical visit and ≥1 anti-inflammatory drug) OR (≥2 anti-inflammatory drugs), over 1 year: -Medicaid children	72 (69-75)	93 (92-94)	76 (73-79)	92 (91-93)
	(≥4 pharmacy claims) OR (≥1 hospitalization or ≥1 ED visit) OR (≥1 ambulatory medical visit) OR (≥1 anti-inflammatory drug), over 1 year: -Medicaid children	92 (90-94)	80 (79-82)	59 (56-61)	97 (96-98)
	(≥4 pharmacy claims) OR (≥1 hospitalization or ED visit) OR (≥2 ambulatory medical visits) OR (≥1 anti-inflammatory drug), over 1 year: -Medicaid children -ConnectiCare children	87 (85-89) 84 (-)	89 (88-90) 92 (-)	70 (67-73) 38 (-)	96 (95-96) 99 (-)
	(≥1 hospitalization or ≥1 ED visit) OR (≥2 ambulatory medical visits) OR (≥1 anti-inflammatory drug), over 1 year: -Medicaid children	86 (84-88)	90 (89-91)	72 (70-75)	96 (95-96)
	(≥1 hospitalization or ≥1 ED visit) OR (≥3 ambulatory medical visits) OR (≥1 anti-inflammatory drug), over 1 year: -Medicaid children -ConnectiCare children	84 (81-86) 78 (-)	93 (92-94) 93 (-)	79 (76-81) 41 (-)	95 (94-96) 99 (-)

Abbreviations: ATC: Anatomical Therapeutic Chemical Classification System; dx: diagnosis; ED: Emergency department; ICS: Inhaled corticosteroids; LABA: Long-acting beta2-agonists; LTRA: leukotriene antagonist receptors; OCS: Oral corticosteroids; SABA: Short-acting beta2-agonists; y: years old.

*Ambulatory medical visits, ED visits and hospitalizations refer to medical encounters that have an asthma diagnosis

**When applicable, validity statistics were rounded to the nearest integer

[†]The first algorithm of the “probable asthma” category correspond to the definition of the Council of State and Territorial Epidemiologists; the other two algorithms correspond to variations of this definition.

[‡]The first algorithm of the “persistent asthma” category correspond to the definition of the Health Plan Employer Data and Information Set; the other seven algorithms correspond to variations of this definition

Table 4. Diagnostic codes and medications used in algorithms of retained studies

Author, year	Codes used and medications (if applicable)
Andrade <i>et al.</i> , 2013 (32)	-ICD-9-CM: 493-493.92
Bechtold <i>et al.</i> , 2012 (34)	-Selective beta2-adrenergic agonists (ATC: R03AC) and adrenergics in fixed combination (ATC: R03AK)
Bianchi <i>et al.</i> , 2011 (35)	-Drugs belonging to the R03 main therapeutic group of the ATC
Biffi <i>et al.</i> , 2017 (33)	For the first operational definition in Table 1: -ICD-9-CM: 493; Exemption code: 007.493 -ATC: R03AK07, R03AK06, R03AC02, R03CC02, R03AC04, R03CC04, R03BA01, R03BA05, R03BA03, R03BA02, R03BA08, R03BC01, R03BC03, R03DA04, R03DC03 For the second and third operational definitions in Table 1: -ICD-9-CM: 493 -ATC: R03AC12, R03AC13, R03AK07, R03AK06, R03AC02, R03CC02, R03AC04, R03CC04, R03BA01, R03BA05, R03BA03, R03BA02, R03BC01, R03BC03, R03BB01, R03BB02, R03DA04, R03DC01, R03DC03, H02
Blais <i>et al.</i> , 2006 (12)	-ICD-9: 493.0; 493.1; 493.9
Bronstein <i>et al.</i> , 2000 (27)	-ICD-9: 493 -CPT-4: 94640; 94650; 94651; 94664; 94655
Dore <i>et al.</i> , 2014 (29)	-ICD-9: 493.xx
Dombkowski <i>et al.</i> , 2012 (28)	-ICD-9-CM: 493.0, 493.1, 493.2, 493.8, 493.9
Gershon <i>et al.</i> , 2009 (20)	-OHIP: 493
Hajibandeh <i>et al.</i> , 2017 (38)	-HES comorbidity codes: Not specified
Huzel <i>et al.</i> , 2002(21)	-ICD-9: 490, 491, 492, 493, 496
Kozyrskyj <i>et al.</i> , 2009 (22)	-ICD-9-CM; Controller medications: Not specified
Lix <i>et al.</i> , 2006 (23)	-ICD-9-CM: 493, -ATC: M02AA, M02AB01, M02AC, M02AX03, M04AA, R03AA01, R03AB02, R03AB03, R03AC02, R03AC03, R03AC04, R03AC08, R03AC12, R03AC13, R03AK01, R03AK03, R03AK04, R03AK06, R03BA01, R03BA02, R03BA03, R03BA05, R03BA06, R03BB01, R03BC01, R03BC03, R03CB01, R03CB03, R03CC02, R03CC03, R03CC07, R03CC53, R03CK, R03DA02, R03DA04, R03DA05, R03DA43, R03DA53, R03DA54, R03DA55, R03DA74, R03DB05, R03DC01, R03DC03, R06AX17, M02AA, M02AB01, M02AC, M02AX03, M04AA
Lujic <i>et al.</i> , 2017(36)	-ICD-10-AM: J45, J46 -ATC: R03AC02, R03AC03, R03AC12, R03AC13, R03AK06, R03BA01, R03BA02, R03BA05, R03BB01, R03BC01, R03BC03, R03CC02, R03CC03, R03DA04, R03DC03

Moth <i>et al.</i>, 2007(37)	-ATC: R03BA01, R03BA02, R03BA05, R03AC02, R03AC03, R03AC04, R03CC02, R03CC03, R03AC12, R03AC13, R03CC12, R03AK06, R03AK07, R03DC03, R03BC01, R03AK03, R03AK04, R03BB01, R03BB04, R03DA04
Omand <i>et al.</i>, 2019 (25)	-ICD-10: J45, J46 -OHIP: 493
To <i>et al.</i>, 2006 (24)	-OHIP: 493
Vollmer <i>et al.</i>, 2004 (30)	-ICD-9: Not specified
Wakefield <i>et al.</i>, 2006 (31)	-ICD-9: 493
Wilchesky <i>et al.</i>, 2004 (26)	-ICD-9: 493.0;- 493.9

Abbreviations: ATC: Anatomical Therapeutic Chemical Classification System; CPT-4: Current Procedures Terminology, 4th Edition; HES: Hospital Episode Statistics; ICD-9: International Statistical Classification of Diseases and Related Health Problems, Ninth Revision; ICD-9-CM: International Statistical Classification of Diseases and Related Health Problems, Ninth Revision, Clinical Modification; ICD-10: International Statistical Classification of Diseases and Related Health Problems, Tenth Revision; ICD-10-AM: International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification