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RESEARCH ARTICLE

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Validity of asthma diagnoses and patterns of anti-asthmatic drug use in a cohort of 2053 Danish children

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Abstract

Background and Aims: When investigating and treating asthma in children, diagnosing must be precise and valid. There is a need for studies researching asthma in children showing how to use registry-based, epidemiological data. We examined the feasibility and validity of using anti-asthmatic drug prescription data to identify children with asthma and assessed medication patterns in children with and without confirmed asthma.

Methods: We used population-based Danish prescription data and hospital discharge registries to identify all children aged 0 to 14 years who had redeemed at least one prescription for an inhaled anti-asthmatic drug. Individual asthma cases were validated by hospital discharge information and by their treating general practitioners according to international asthma guidelines.

Results: In total, 2053 children, out of a population of 20181, had redeemed at least one prescription of any inhaled anti-asthmatic drug. The positive predictive value (PPV) of having two different asthma medications prescribed in 1 year was 80.2% for presence of true asthma, with a sensitivity of 59%. Corresponding estimates of PPV/sensitivity of at least one prescription for an inhaled corticosteroid (ICS) were 79% and 58%, respectively, while the true asthma PPV with at least one LABA prescription increased to 97%. Among children with confirmed asthma, one-third had not used Beta2-agonist therapy as part of their treatment. Conversely, among children without confirmed asthma, 40% were prescribed a minimum of two prescriptions for any kind of inhaled anti-asthmatic drug, and 12% and 9% used an ICS or Leukotriene receptor antagonist, respectively.

Conclusions: Anti-asthmatic drug prescription data could be used to identify children with true asthma, with reasonable accuracy. The observed pattern of anti-asthmatic medication usage among children with and without confirmed asthma suggests that there is room for therapeutic improvement.

1 | INTRODUCTION

Asthma is a frequent disorder in children, with a reported prevalence varying from 4% to 22%.[1-5] In screening studies, approximately one-third of children with asthma have not been previously diagnosed with asthma.[3] Asthma medication prescription data have been used as a surrogate marker of asthma in attempts to estimate the prevalence of asthma in children. However, a recent study including 1744 children referred from general practitioners (GPs) to hospital specialist care for suspected asthma showed that approximately 30% of children not having specialist-confirmed asthma were treated with inhaled corticosteroids (ICS) by their GP, and conversely, 33% of the children having specialist-confirmed asthma were not treated with any asthma medication by the GP.[3] Thus, use of asthma medications may be nonspecific and non-complete for the presence of true asthma in any population, but the exact validity in population-based settings is unknown.

Several industrialized countries, including Denmark, have comprehensive administrative databases on medication prescriptions, which may be a strong resource in identifying children with asthma.[4,6] In the present validation study, we aimed to utilize such data to identify all anti-asthmatic drug users among children in a well-defined rural area. We then set out to identify children with true asthma, diagnosed and validated by GPs and hospital doctors in the same geographical area, using the asthma definition of British Thoracic Society (BTS) and Global Initiative for Asthma (GINA) and national Danish guidelines.[7-9] We examined the validity and completeness of using prescription data to identify true asthma. We further investigated the pattern of asthma medication usage among children with and without confirmed asthma. We hypothesized that use of multiple anti-asthmatic drug prescriptions and use of drugs such as ICS or Leukotriene receptor antagonists would be rare in children without true asthma.

2 | MATERIAL AND METHODS

2.1 | Setting

This study was a registry-based cross-sectional study, conducted in the Central Denmark region, Viborg County (population, 96 000 inhabitants, 20 181 children/youth 0-14 years of age). Denmark is a welfare state, with tax-financed universal access to health services. Except for emergencies, patients' initial contact with the health care system is through their GPs, who act as gatekeepers and provide referrals to hospitals and specialist physicians as necessary.[10] Patients are normally registered with a single GP, and records from each GP can be assumed complete for an individual patient.

2.2 | Data sources

Data in our study were collected from:

- The Aarhus University Prescription Database[10]
- The Danish National Patient Register[11]
- Medical charts and validated diagnostic sheets (case record forms) from GPs
- Medical charts from hospital specialist outpatient clinics

The Aarhus University Prescription Database[10] collects data on reimbursed medications dispensed at all community pharmacies of the Central Denmark Region and covers all inhabitants of Viborg County. It includes information on number and type of drug according to Anatomical Therapeutic Chemical classification system (ATC-code), date of purchasing and dispensing of the prescribed drug, the GP's unique service provider number, and the patient's Danish Personal Identification number (CPR number).

2.3 | Study population

The universal use of CPR numbers, assigned to all Danish citizens at birth or immigration, enabled exact linkage between these data sources.

We identified a baseline study population of children with potential asthma, as follows:

1) All children aged 0 to 14 years who were resident in the Viborg area, corresponding to years of birth between 1996 and 2010, and who according to the population-based Aarhus University Prescription Database[10] had redeemed any type of inhaled anti-asthmatic drug, identified by ATC-code (Table 1), during the 1-year period between 1 January 2010 to 31 December 2010. The study focused on children aged 0 to 14 years because, at the time the study was conducted, this was the population defined to be controlled in pediatric care. A 1-year period was selected to minimize seasonal variation in the asthmatic symptoms and asthma medication use. Prescriptions for liquid/oral mixture Beta2-agonists were not included. Of 89 GPs with a clinical practice in the Viborg area, 81 GPs accepted to be included in the study.
2) All children with asthma diagnosis discharged from the pediatric department or followed in the hospital pediatric specialist outpatient clinic at Viborg hospital, which serves all inhabitants of Viborg County. Diagnoses were based on diagnosis codes classified according to World Health Organization's (WHO) International Classification of Diseases, 10th revision (ICD-10), in their electronically medical charts from 1 January 2010 to 31 December 2010. Asthma diagnosis codes, Table 1.
3) In all these children, confirmed asthma diagnosis was based on international guidelines, Table 2.[7,8] During the validation process (see below), GPs had the possibility to add any children from their practice who had known guideline-confirmed asthma, but had not been prescribed with asthma medication use in the Aarhus University Prescription Database.

2.4 | Validation of asthma diagnoses

As part of a larger unpublished quality control project taking place during 2011 to 2015, GPs in Viborg County attended educational

TABLE 1 List of anti-asthmatic drugs (ATC-codes) and primary diagnoses (ICD10)

Anti-asthmatic drugs (ATC-codes) used to identify children with potential asthma:
R03BA inhaled corticosteroid
R03BA01 beclometasone
R03BA02 budesonide
R03BA05 fluticasone
R03BA07 mometasonfuroat
R03AC short- and long acting Beta2 agonist (minus liquid)
R03AC02 salbutamol
R03CC02 salbutamol
R03AC03 terbutaline
R03CC03 terbutalin
R03AC04 fenoterol
R03AC12 salmeterol
R03CC12 bambuterol
R03AC13 formoterol
R03DC leukotrien receptor antagonist
R03DC03 montelukast
R03AK kombinationspræparater
R03AK06 fluticasonpropionat, salmeterol
R03AK07 budesonid, formoterol
Link: http://www.whocc.no/atc_ddd_index/
Primary diagnoses (ICD10) used for identifying children with asthma in the hospital specialist outpatient clinics:
J45 asthma
J45.0 allergic asthma
J45.1 nonallergic asthma
J45.8 mixed asthma
J45.9 asthma, unspecified
J46.9 status asthmaticus
Z038 + one of the codes above as secondary diagnosis

sessions in 2010 before this project started on how to correctly diagnose asthma based on the international guidelines.[7,8] The GPs afterwards received from the investigators a list of children registered in their practice who had redeemed at least one prescription of inhaled anti-asthmatic drugs (Table 1) during 2010. GPs then evaluated each individual patient on their complete list with regard to fulfilling the criteria of true asthma diagnosis (Lung function test, Beta-2-agonist reversibility test, level of asthma control according to international guidelines). The GPs then added any children with asthma diagnoses that were not on the list and sent results back to the investigators. Thus, GPs fulfilled a case record form for all children in order to verify the asthma diagnosis. When still in doubt of presence or absence of asthma in any patient, the child was referred to the hospital specialist outpatient clinic at Viborg Hospital in order to verify the asthma diagnosis. The GPs were paid a fee of 2500 DKR (335 EUR) for their participation in the project. Children who had received their asthma diagnosis by specialists at Viborg Hospital were defined as having true asthma.[12] Thereby, all children followed by either hospital specialists or GPs had their asthma diagnosis verified and validated according to international guidelines.

2.5 | Statistical analysis

The positive predictive value (PPV) of use of different anti-asthmatic drug regimens for the presence of true asthma was calculated as a proportion (ie, the numerator containing the number of children with confirmed asthma based on hospital diagnoses or GP validation, and the denominator containing the total number of children with the drug regimen). Sensitivity was calculated as the proportion of all children with confirmed asthma that were captured by different anti-asthmatic drug regimens. Statistical analysis was processed using STATA version 12.

2.6 | Ethics

The study was approved by the Danish Data Protection Agency (2007-58-0010) and by the Danish National Board of Health (7-604-04-2/245).

3 | RESULTS

In total, 2053 children were included in the study from hospital and GPs. Of these, 1990 children were included in the cohort based on having redeemed any type of inhaled anti-asthmatic drug at least once in 2010. Another 63 children were included by the GPs as having asthma without having had any type of inhaled anti-asthmatic drug before. Of the 2053 children, 1365 (66%) children proved to have confirmed asthma. Of children having confirmed asthma (n = 1365), 32% (435/1365) were followed by hospital specialist physicians and 68% (930/1365) exclusively by their GP. Thus, 688 children (34%) did not have confirmed asthma even though they had redeemed any type of inhaled anti-asthmatic drug at least once. Age and sex of children with and without confirmed asthma are shown in Table 3, showing that the proportion of young children (0-5 years old) was higher in the unconfirmed versus confirmed asthma group.

TABLE 2 Gold standard for asthma

Gold standard for asthma: Fulfillment of the following criteria using GINA guidelines/BTS guidelines[7,8]:
1. Clinical symptoms such as episodic breathlessness, wheezing, cough, or chest tightness, recorded as daytime symptoms or nighttime symptoms +
2. Lung function measurement (spirometry) showing FEV1% < 80% +
3. At least one of the following: a. Positive reversibility test with a bronchodilator: FEV1 (forced expiratory volume in one second) increase >12% b. Positive exercise test: Increase of FEV1 > 12% c. Pathological mannitol test or methacholine test

TABLE 3 Demographic (age and sex) information of children with confirmed asthma and children without confirmed asthma in Viborg County, 2010

Age	Children with Confirmed Asthma (N/%) N = 1365	Children without Confirmed Asthma (N/%) N = 688	All Children with Potential Asthma N = 2053
0-5	736 (54.0)	511 (74.3)	1247
6-11	410 (30.0)	136 (19.7)	546
12-14	219 (16.0)	41 (6.0)	260
Males	866 (63.4)	379 (55.1)	1245
Females	499 (36.6)	309 (44.9)	808
Total	1365 (100)	688 (100)	2053

3.1 | Medication use among children with confirmed asthma

Of the patients with a verified asthma diagnosis, 96.6% (1319/1365) had redeemed at least one prescription for any anti-asthmatic drug (Table 4). Of note, only 76.2% (1040/1365) of patients with verified asthma had redeemed ≥1 prescription of an inhaled Beta2 agonist, meaning that approximately one-quarter of children with verified asthma did not redeem a Beta2 agonist prescription, ie, had preventive anti-asthmatic treatment without Beta2 agonist treatment. Of all children with true asthma, 59.0% (806/1365) had both Beta2 agonist and ICS (or another preventive medication) prescribed during the study period. The vast majority of children with verified asthma received treatment with either ICS or Leukotrien receptor antagonists. Among children with confirmed asthma who redeemed at least two prescriptions for inhaled Beta2-agonists, 79% (399/505) also redeemed prescriptions of either Leukotrien receptor antagonists and/or ICS.

3.2 | Medication use among children with no confirmed asthma

Of the patients without a verified asthma diagnosis, 97.5% (671/688) had at least one inhaled anti-asthmatic drug prescription during the study period, and 40.4% (278/688) redeemed a minimum of two prescriptions. Of note, 6.3% (43/688) of children with no asthma had redeemed three or more prescriptions of Beta2 agonist in 1 year, and 12.4% (85/688) of the children with no asthma redeemed two or more prescriptions for either ICS or montelukast.

3.3 | Validity of asthma treatment for defining true asthma

In general, there was an increasing probability of having true asthma the more prescriptions redeemed, as expected (Table 5). Thus, 79.3% (794/1001) of children having redeemed at least one prescription for ICS had true asthma, increasing to 90.6% (348/384) of those who

TABLE 4 Pattern of anti-asthmatic medication use in children with confirmed asthma and without confirmed asthma in Viborg County, 2010

Prescription Regimen in 2010	Children with Confirmed Asthma (% of All Confirmed Asthma)N = 1365	Children without Confirmed Asthma (% of All Unconfirmed Asthma)N = 688
0 prescription for any R03 drug[a]	46 (3.4)	17 (2.5)
≥ 1 prescription for any R03 drug	1319 (96.6)	671 (97.5)
≥ 2 prescriptions for any R03 drug	1017 (74.5)	278 (40.4)
≥ 2 prescriptions for two different R03 drugs	806 (59.0)	199 (28.9)
≥ 1 prescription for ICS[b]	794 (58.2)	207 (30.1)
≥ 2 prescriptions for ICS	511 (37.4)	85 (12.4)
≥ 3 prescriptions for ICS	348 (25.5)	36 (5.2)
≥ 1 prescription for inhaled Beta2 agonist [c]	1040 (76.2)	557 (81.0)
≥ 2 prescriptions for inhaled Beta2 agonist	505 (37.0)	143 (20.8)
≥ 3 prescriptions for inhaled Beta2 agonist	274 (20.1)	43 (6.3)
≥ 1 prescription for montelukast[d]	459 (33.6)	129 (18.8)
≥ 2 prescriptions for montelukast	330 (24.2)	60 (8.7)
≥ 3 prescriptions for montelukast	245 (17.9)	37 (5.4)
≥ 1 prescription for LABA[e]	94 (6.9)	2 (0.3)
≥ 2 prescriptions for LABA	79 (5.8)	0 (0)
≥ 3 prescriptions for LABA	66 (4.8)	0 (0)

[a]ATC R03 drug: All inhaled anti-asthmatic drugs.

[b]Inhaled corticosteroid (ICS): ATC R03B.

[c]Inhaled Beta2 agonists: ATC R03AC02, R03AC03, R03CC.

[d]Montelukast (leukotrien antagonist): ATC R03DC.

[e]LABA—long-acting beta-adrenoceptor agonist: ATC R03AC04, R03AC05, R03AC12, R03AC13, R03AC18, R03AK06, R03AK07, R03AK08, R03AK10, R03AK11.

TABLE 5 Positive predictive value (PPV) and sensitivity for true asthma of different drug regimens

Prescription regimen in 2010	Number of Children in Total with Specified Prescribed Treatment	Number of Children with Confirmed Asthma	PPV with 95% CI	Sensitivity with 95% CI
≥ 1 prescription for any R03 drug[a]	1990	1319	66.3 (64.2;68.3)	96.6 (95.5;97.5)
≥ 2 prescriptions for any R03 drug	1295	1017	78.5 (76.2;80.7)	74.5 (72.1;76.7)
≥ 2 prescriptions for two different R03 drugs	1005	806	80.2 (77.6;82.5)	59.0 (56.4;61.6)
≥ 1 prescription for ICS[b]	1001	794	79.3 (76.7;81.7)	58.2 (55.5;60.8)
≥ 2 prescriptions for ICS	596	511	85.7 (82.7;88.3)	37.4 (34.9;40.0)
≥ 3 prescriptions for ICS	384	348	90.6 (87.3;93.2)	25.5 (23.3;27.9)
≥ 1 prescription for inhaled Beta2[c]	1597	1040	65.1 (62.8;67.4)	76.2 (73.9;78.4)
≥ 2 prescriptions for inhaled Beta2	648	505	77.9 (74.6;81.0)	37.0 (34.5;39.6)
≥ 3 prescriptions for inhaled Beta2	317	274	86.4 (82.2;89.8)	20.1 (18.0;22.3)
≥ 1 prescription for montelukast[d]	588	459	78.1 (74.5;81.2)	33.6 (31.2;36.2)
≥ 2 prescriptions for montelukast	390	330	84.6 (80.7;87.9)	24.2 (22.0;26.5)
≥ 3 prescriptions for montelukast	282	245	86.9 (82.4;90.3)	17.9 (16.0;20.1)
≥ 1 prescription for LABA[e]	96	94	97.9 (92.7;99.4)	6.9 (5.7;8.4)
≥ 2 prescriptions for LABA	79	79	100.0 (95.4;100.0)	5.8 (4.7;7.2)
≥ 3 prescriptions for LABA	66	66	100.0 (94.5;100.0)	4.8 (3.8;6.1)

[a]ATC R03 drug: All inhaled anti-asthmatic drugs.

[b]Inhaled corticosteroid (ICS): ATC R03B.

[c]Inhaled Beta2 agonists: ATC R03AC02, R03AC03, R03CC.

[d]Montelukast (leukotrien antagonist): ATC R03DC.

[e]LABA—long-acting beta-adrenoceptor agonist: ATC R03AC04, R03AC05, R03AC12, R03AC13, R03AC18, R03AK06, R03AK07, R03AK08, R03AK10, R03AK11.

had redeemed three or more prescriptions of ICS. Most children (97.9%, 94/96) with at least one prescription to LABA treatment had verified asthma.

When assessing different types of drug regimens to find the best model that would include as many children as possible with a validated asthma diagnosis (sensitivity), and at the same time exclude as many false positives as possible (high PPV), our results suggested the following models:

1. A PPV of 80.2% and sensitivity of 59.0% for identifying true asthma when including children with at least two prescriptions in 1 year that include two different types of asthma medication
2. A PPV of 79.3% and sensitivity of 58.2% for identifying true asthma when including children with at least one prescription for an ICS.

4 | DISCUSSION

Our study has characterized the pattern of asthma medication usage among children with true asthma, ie, verified doctor diagnosed asthma, in a Danish rural area. Our research hypothesis was that physicians, in general, followed guidelines for anti-asthmatic treatment. For example, children with confirmed asthma who had at least two prescriptions for inhaled Beta2-agonists should also be treated with Leukotrien receptor antagonists and/or ICS within that year, which was the case in 79% of the children.

Children without asthma may show symptoms consistent with asthma, where Beta2 treatment attempts may be clinically useful one or two times in order to test a positive effect on symptoms, thus confirming likely asthma or not. Our data showed that 93.7% (645/688) of children without confirmed asthma had a maximum of two prescriptions on inhaled Beta2-agonists within 1 year, which we would deem clinically acceptable. Of greater concern, one out of 10 children with no asthma was treated with preventive anti-asthmatic treatments more than once within 1 year. Thus, children without asthma did redeem a prescription on two or more separate occasions for either Leukotrien receptor antagonists in 12.4% (85/688) or ICS in 8.7% (60/688) of the cases. One ICS or Leukotrien treatment attempt could prove useful in addition to treatment attempts with Beta2-agonists; however, several attempts during a year, without being able to make a valid asthma diagnosis, may point to room for improvement of asthma therapy. Approximately one in three children with verified asthma did not redeem a Beta2 agonist prescription, even though most of them had redeemed preventive anti-asthmatic treatment prescriptions. This could imply that the asthma children were well-controlled and properly treated with prevention medication, and this may be due to the fact that one inhaler may entail doses for a longer period. However, it is important to ensure that no children are without acute asthma symptom therapy. These findings are in opposition to previous studies in Denmark on young adult asthmatics, which demonstrated a continuing inadequate use of ICS with a consistent and high use of reliever therapy, which was associated with uncontrolled asthma.[13,14] The study findings are coherent with a newly published study in Denmark, concluding that an algorithm of asthma defined by disease-specific hospital contacts and/or ≥ 2 filled prescriptions within 12 months results in a PPV of 73.3%, although not specifying ATC codes of prescription data, which may explain why this study captures an even higher PPV, of 80.2%.[15]

Our study estimated the predictive value of different asthma medications for true asthma in the age group 0 to 14 years by using register-based prescription data as a proxy for asthma. We found that some asthma medication can be used as a reasonable proxy for true asthma diagnoses. This may be specific to Danish databases or prove itself as a general improvement of validity of data from registers when comparing to previous studies in Germany and The Netherlands.[16-18] When choosing the "cut-off" of at least two prescriptions redeemed, not for the same drug but for two different R03 drugs, the PPV was 80%, with a moderate sensitivity of close to 60%. Similar accuracy was found with just one prescription for ICS.

4.1 | Strengths and limitations

Asthma is a clinical diagnosis made by physicians on the basis of a patient's symptoms and medical history, a clinical examination, and exclusion of differential diagnosis. A strength of the study was that asthma diagnoses were individually validated in all children by doctors specifically trained and educated in asthma diagnosing guidelines.

Our use of complete prescription registries and the validation process afterwards regarding asthma diagnosis reduced any selection and recall bias. We believe that our validation data may be generalized to national populations of individuals with childhood asthma due to the fact that Viborg rural area is a larger commune of Jutland and is inhabited by 2% of the Danish population, and also by the fact that almost all GPs, 91% (81/89) within the rural area of Viborg, were included. However, we did not include all children in Viborg County to be screened/examined for asthma, and completeness for true asthma may, thus, be underestimated due to undetected children.

5 | CONCLUSION

Anti-asthmatic drug prescription data in Viborg County could be used to identify children with confirmed asthma with reasonable accuracy. The observed pattern of anti-asthmatic medication usage among children with and without true asthma suggests that there is still room for therapeutic improvement. The outcome showing a PPV of 80.2% and a sensitivity of 59% of the cohort of children with confirmed asthma established in our validation study may be used for future longitudinal population-based surveillance and research. This study yields results that show how future studies researching asthma in children can benefit from using registry-based epidemiological data.

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CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

All authors significantly contributed to the article and approved the final version for submission.

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