

Validation of asthma and eczema in population-based Swedish drug and patient registers

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ABSTRACT

Purpose Validated measures of asthma and eczema at the population level remain a challenge. Our aim was to ascertain if register-based information on asthma/eczema medication can function as a proxy for an asthma/eczema diagnosis and to validate register-based asthma diagnoses.

Methods Information was requested on all 0–45-year-old individuals with reported asthma/eczema medication and/or diagnoses in the Swedish Prescribed Drug Register and National Patient Register, between July 2005 and December 2009 ($N = 250\,691$). Medical records for 1952 randomly selected individuals were reviewed to estimate the proportion of individuals with the following: (1) asthma/eczema medication that fulfilled predefined criteria of asthma/eczema (positive predictive value (PPV)) and (2) a register-based asthma diagnosis verified as asthma by predefined criteria.

Results Positive predictive value for asthma by predefined criteria ranged between 0.75 (95%CI: 0.70–0.78) to 0.94 (95%CI: 0.91–0.96), depending on age group. In pre-school children, PPV for asthma in combination with obstructive bronchitis was 0.87 (95%CI: 0.83–0.90), and PPV for eczema was estimated to 0.45 (95%CI: 0.38–0.51). Eighty percent of children 0–4.5 years and 99% of children >4.5–17 years with a register-based diagnosis of asthma were verified as asthmatics.

Conclusion Asthma medication is a suitable proxy for asthma in older children and adults; the same approach is insufficient for eczema. This validation study of two Swedish registers opens for future large nation-wide register-based studies on asthma. Copyright © 2013 John Wiley & Sons, Ltd.

KEY WORDS—allergic diseases; asthma outcome research; asthma pharmacology; disease proxy; nationwide; prescription prevalence; pharmacoepidemiology

Received 7 December 2012; Revised 2 April 2013; Accepted 29 April 2013

INTRODUCTION

Asthma and eczema are two of the most common chronic childhood diseases in the world.^{1,2} Asthma is an inflammatory disease of the airways with a prevalence of about 8–10% in children and 6–8% in adults in Sweden.^{3,4} Eczema, manifesting as chronic itchy flexural rashes, affects about 20% of all Swedish children.²

Valid measures of asthma and eczema at the population level remain a challenge.⁵ Most epidemiological studies investigating asthma and eczema have previously used questionnaires to identify these diseases.⁶ Questionnaires are often restricted to specific areas or age groups, which limit the generalizability to other study populations, and can also be susceptible to culture-related and language-related issues associated with translation and interpretation,^{7,8} which can lead to misclassification bias. Parental answers to questionnaires that are obtained retrospectively can further lead to recall bias of both exposure and outcome, which can affect reported associations.⁹ These types of biases

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can be avoided by using population-based register data. Because of ethical, economical and practical reasons, a standardized clinical examination of individuals with and without asthma/eczema is not feasible in large-scale studies. Thus, validated population-based register data can function as a proxy, when aiming to study the diseases in the total population.

The Swedish National Board of Health and Welfare (NBHW) holds several population-based health registers, such as the Swedish Prescribed Drug Register (SPDR)¹⁰ and the National Patient Register (NPR),¹¹ covering the entire Swedish population (nine million inhabitants). Since July 2005, all dispensed prescriptions are reported to the SPDR. All diagnoses from the in-patient care and 75% of specialized out-patient care are reported to the NPR since 1964 and 2001, respectively, whereas diagnoses from primary health care centres (PHCC) are not recorded on a national level. To identify individuals with asthma and eczema in Sweden that have visited a physician at a PHCC, these diagnoses could be conveniently identified in the SPDR, which allows identification of specific drugs for treatment of specific diseases.

Previous studies have validated asthma medication as a proxy for asthmatic disease in children^{12–15} and adults^{15–17} by reviewing medical records from general practitioners (GPs)^{13,16,17} or through retrospective questionnaires to GPs¹² and paediatricians¹⁴ in limited regions. Others have suggested that prescription prevalence of asthma medication could function as a measure of disease prevalence in children¹⁸ and adults.¹⁹ Until now, there is no population-based study that has used randomly selected medical records on a national level to validate an asthma diagnosis with predefined criteria based on dispensed prescriptions of asthma medications. Some Swedish studies have already used asthma medication as a proxy for asthmatic disease,^{20–23} but so far, no one has validated the Swedish data from the SPDR. Additionally, the authors have not been able to identify any study that has investigated the opportunity of using prescription data on eczema medication as a proxy for eczema. Moreover, although several diagnoses in the NPR have been validated²⁴ and asthma diagnosis has been used in previous studies,^{20,24} the quality of the diagnosis has not yet been validated.

To enhance the strength and quality of register-based research and to obtain generalizable findings in large populations, validation of register data is needed. Therefore, this study aimed the following: (1) to describe the utilization of asthma/eczema medication in Sweden; (2) to validate if medication for asthma/eczema can function as a proxy for an asthma/eczema diagnosis respectively, by reviewing medical records corresponding

to dispensed medications in the SPDR, according to doctor diagnoses and predefined criteria by the Swedish Paediatric Society's section for Allergy²⁵; and (3) to validate asthma diagnoses in children in the NPR, by investigating how a reported diagnosis of asthma corresponds to set criteria.²⁵

METHOD

Study design and population

This was a nationwide population-based register study using information from the SPDR, the NPR and medical records from PHCC and hospitals all around Sweden.

The SPDR is one of the largest population-based drug registers in the world.¹⁰ It provides complete data on dispensed drugs regardless of age, gender, prescribing physician and reimbursement status. All pharmaceuticals are classified according to the Anatomical Therapeutic Chemical classifications system (ATC). The NPR includes information on primary and secondary diagnoses, according to the International Classification of Diseases (ICD) system. The universal use of the personal identity number (PIN)²⁶ enables a linkage between the SPDR and NPR.

Encrypted information on all individuals, 0–45 years of age, who had filled at least one prescription of asthma and/or eczema medication (aim 1) and/or had been given a diagnosis of asthma (ICD 10 code J45) and/or eczema (ICD 10 code L20) between July 2005 and December 2009, was requested from the NBHW. Information on the patients' age, sex, prescription and dispensing date, data on dispensed item and amount (SPDR) and discharge date (NPR), was also requested. Medications of interest were inhalations of selective β_2 -adrenoreceptor agonists (ATC: R03AC), glucocorticoids (R03BA) and fixed combinations of β_2 -agonists and glucocorticoids (R03AK), leukotriene receptor antagonists (R03DC), glucocorticoids for external use (D07A) and the immunosuppressant tacrolimus (D11AH01) and pimecrolimus (D11AH02). Selective β_2 -adrenoreceptor agonists for systemic use (R03C) were not included.

Figure 1 displays the linkage between the SPDR and the NPR and the inclusion criteria for the study population. To validate asthma/eczema medication in the SPDR as a proxy for an asthma/eczema diagnosis, all individuals with filled prescriptions of asthma/eczema medication without a diagnosis of asthma/eczema in the NPR were identified and grouped on the basis of the age at the date of a given prescription (asthma medication: 0–4.5, >4.5–17, 18–45 years; eczema medication: 0–17 years), as well as number of filled prescriptions and type of prescribed medication. The

VALIDATION OF ASTHMA AND ECZEMA IN SWEDISH REGISTERS

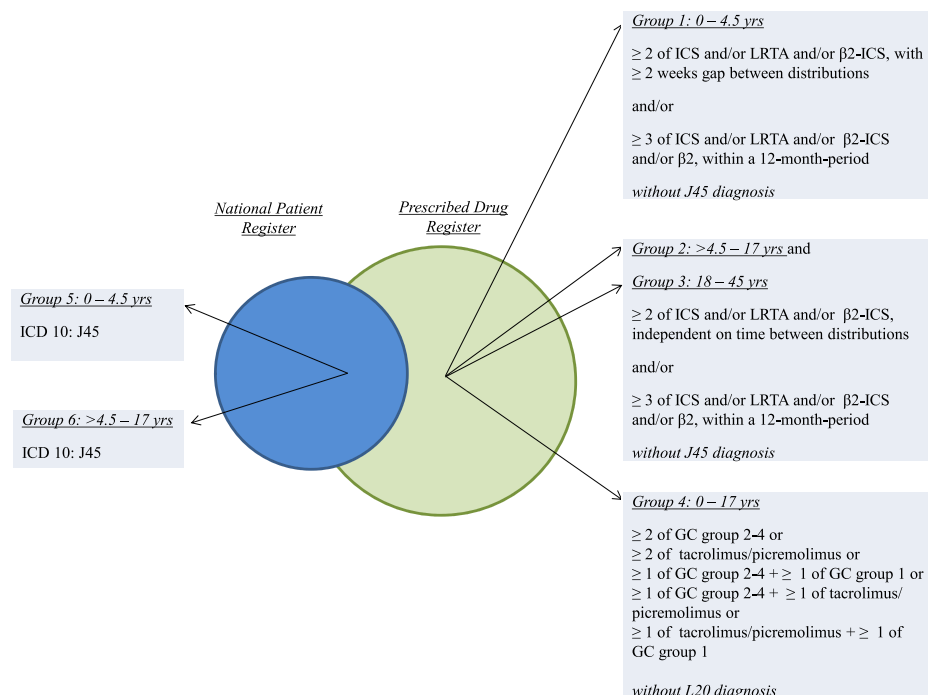


Figure 1. Through a linkage between the Swedish Prescribed Drug Register and National Patient Register, six groups of individuals were identified based on age at prescription, type and number of filled prescriptions of asthma/eczema medication without a diagnosis of asthma/eczema (aim 2: groups 1–4), or based on a diagnosis of asthma independent on history of medication (aim 3: group 5 and 6). The figure displays inclusion criteria for each group (1–6). ICS – Inhalations of corticosteroids (R03BA); LRTA – Leukotriene receptor antagonist (R03DC); $\beta 2$ -ICS – fixed combinations of $\beta 2$ -agonists and corticosteroids (R03AK); $\beta 2$ – inhalations of $\beta 2$ -adrenoreceptor agonists (R03AC); GC – glucocorticoids for external use (1) mild; (2) moderate; (3) potent; (4) very potent (D07A); Tacrolimus – immunosuppressant (D11AH01); Picremolimus – immunosuppressant (D11AH02); J45 – ICD 10 for asthma diagnosis; L20 – ICD 10 for eczema diagnosis.

reason for excluding individuals with a diagnosis of asthma/eczema was to ascertain the possibility of using SPDR as a complementary source of information to the NPR. To avoid one-time asthma medication users, at least two or more dispensed prescriptions were needed, as well as a time frame of 2 weeks between prescriptions for the pre-school children. To validate the diagnosis of asthma in the NPR two groups of children (0–4.5; >4.5–17 years) with a diagnosis of asthma, independent of history of asthma medication were furthermore identified.

Collection and assessment of medical records

A simple random sample (without replacement) of individuals was drawn within each group by the NBHW who then provided us with PINs for the samples. The study participants' medical records corresponding to the dates of prescriptions of the asthma/eczema medication (aim 2), or corresponding to the discharge date from the hospital (aim 3), were requested by a letter to the head of the unit/ward where the patient had been treated. Two reminder letters were sent out before the end of data collection.

The diagnosis that each patient had been assigned by the physician at each consultation connected to the date of the prescribed medication was extracted from the medical records. Diagnoses of special interest for the asthma part were asthma (J45), acute bronchitis/bronchiolitis (J20/J21) and chronic bronchitis/chronic obstructive pulmonary disease (COPD) (J42/J44).

Furthermore, medical records belonging to pre-schoolers (0–4.5 years) and school-age children (>4.5–17 years) in the asthma medication validation and asthma diagnosis validation were combined and reviewed by authors A. Ö. and C. A. according to the criteria of asthma set by the Swedish Paediatric Society,²⁵ where asthma is defined as ≥ 3 obstructive periods before 2 years of age and/or ≥ 1 obstructive period after 2 years of age and/or ≥ 1 obstructive period independent of age when the child has ≥ 1 of the following: eczema, allergy or no improvement between periods of respiratory tract infections. Children under 2 years of age with ≤ 2 asthma-like symptoms during respiratory tract infections and without symptoms between infections were defined as suffering from obstructive bronchitis. Individuals without recorded patient history (e.g. only a renewal

of a prescription) in any medical record were excluded in the analysis of PPV.

Records in the eczema part were firstly reviewed to assess whether the child had the 'umbrella diagnosis' dermatitis, which was defined as either having been assigned the diagnosis unspecific dermatitis (L30.9) by a physician or if having been given either sub-diagnosis of dermatitis such as eczema (L20), allergic/non-allergic contact dermatitis (L23–L25) or seborrhoeic dermatitis (L21) assigned by the physician. Secondly, each assigned sub-diagnosis of dermatitis was analysed separately.

Statistical analysis

To describe the utilization of asthma/eczema medication in Sweden, period prevalence of drug users was estimated as the proportion of individuals in the Swedish population for whom medication was dispensed during year 2008. The numbers of individuals were retrieved from Statistics Sweden.²⁷

Incidence estimates were based on all new users of anti-asthmatic drugs between 2008 and 2009 and estimated person-time based on population data from Statistics Sweden²⁷ with 95% confidence intervals calculated assuming Poisson distribution. The period was based on the waiting-time distribution,²⁸ which is a frequency distribution of first time occurrences of drug use within a time window. Figure 2 shows the monthly frequencies of first appearances of filled prescriptions

for all persons who have redeemed anti-asthmatic prescriptions July 2005–December 2009, according to the appearance of their first filled prescription within the period. In the beginning of the period, there was a mixture of old and new users. The frequencies thereafter decreased until it levels out. At this point, mostly new (incident) users appeared. The period used for incidence estimation has to be beyond this point in time to avoid prevalent users to be included in the calculations.

To validate reported asthma/eczema medication in the SPDR as a proxy for an asthma/eczema diagnosis, positive predictive value (PPV) was estimated as the proportion of children and adults that had been given a diagnosis of asthma/eczema (as well other asthma-like and dermatitis-like diagnoses) in each medication validation group with asthma/eczema medication. PPV was also estimated as the proportion of pre-schoolers and school-age children with asthma medication that fulfilled the criteria of asthma set by the Swedish Paediatric Society. Subgroup calculations of PPV by sex and inclusion criteria (≥ 2 or ≥ 3 prescriptions within different periods) were also performed. The sample size in each group was determined based on an expected PPV of 75% and aim of 95% confidence intervals of $\pm 5\%$ units.

To validate the diagnosis of asthma in children in the NPR, the proportion of children that had been given a

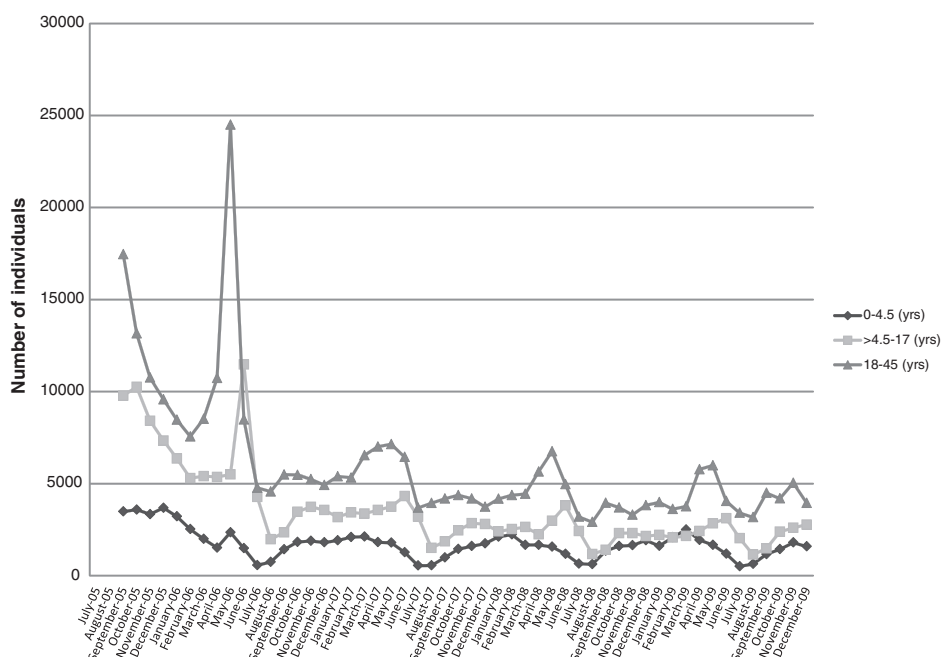


Figure 2. Number of individuals with first time filled prescriptions of ATC group R03 (excluding R03C), for children and adults each month, between July 2005 and December 2009. The years of 2008–2009 were considered in the analysis of incidence.

diagnosis by a physician that fulfilled the criteria of asthma was calculated.

Statistical Analysis Software 9.3 (SAS Institute, Cary, NC) was used for all analyses. The study was approved by the Regional Ethical Review Board in Stockholm, Sweden.

RESULTS

Prevalence and incidence

Table 1 shows the period prevalence of anti-asthmatic drugs in year 2008 in Sweden. In total, 282 826 individuals between 0 and 45 years of age redeemed approximately 890 000 prescriptions of anti-asthmatic drugs. The period prevalence decreased from 7.5% in pre-school children to 6.4% in school-age children and 4.7% in adults. Males were more commonly prescribed asthma medication in childhood, whereas females dominated in adulthood. The most commonly prescribed anti-asthmatic drug in all age groups was inhalations of selective β_2 -adrenoreceptor agonists. The table further presents the number of individuals with one to four or more dispensed items of any asthma medication during 2008. Approximately 80% of the pre-school children had two or more dispensed items and corresponding numbers were 66% and 62% for school-age children and adults.

Table 1 also displays the numbers for drugs used to treat eczema. The period prevalence of drugs against eczema also decreased with increasing age. Mild glucocorticoids (GC) was the most commonly filled drug against eczema in children 0–4.5 years, moderate GC in children >4.5–17 years and potent GC in adults.

Figure 2 presents the number of 'new' unique subjects having redeemed anti-asthmatic drugs for each month July 2005–December 2009. The incidence of new anti-asthmatic drug users was assessed after a wash-out period of 30 months. The estimated number of person-years 2008–2009 in pre-school children were 980 011, in school-age children 2 604 623 and in adults 6 874 703. In total, 36 263 pre-school children were defined as new users during 2008–2009 thus rendering an incidence of 3.70/100 person-years (95% Confidence Interval (CI): 3.66–3.74). For school-age children, the number of new users was 55 234 corresponding to an incidence of 2.12/100 person-years (95%CI: 2.10–2.14), and in adults, 102 454 users were found to give an incidence of 1.49/100 person-years (95%CI: 1.48–1.50).

Asthma medication as a proxy for asthma diagnosis

Table 2 displays number of identified individuals in each study group and number of individuals for whom medical records were requested and retrieved. In total,

250 691 individuals fulfilled the inclusion criteria, and requests for 2600 patients' medical records were sent out. In total, 998 units/wards for the asthma medication validation, 330 for the eczema medication validation and 119 for the asthma diagnosis validation were contacted. We obtained data on 1952 patients (75%). The table further presents the overlap of children with an asthma diagnosis in the NPR and their medications in the SPDR. Approximately 95% of the children included in the validation of asthma diagnosis in the NPR had filled at least one prescription of asthma medication, whereas about 65% of the individuals fulfilled the criteria of asthma medication that was used in the validation of the SPDR for groups 1 and 2 (Figure 1).

Table 2 also shows the response rates of received medical records, where the highest response rates were found in pre-schoolers (0–4.5 years: 87%) and school-age children (>4.5–17 years: 83%) in the validation of asthma diagnoses in the NPR. The lowest response rate of 66% corresponds to school-age children in the asthma medication validation.

Reasons for no response were as follows: (1) head of unit did not want to participate in study; (2) health care centre had ceased to exist; (3) no medical charts could be found at the unit; and (4) requests did not reach the recipients.

Table 3 displays the PPV in the asthma medication validation, for a doctor diagnosis of asthma and other 'asthma-like' diseases such as acute/chronic bronchitis in received medicals records. PPV for a doctor-diagnosed asthma was 89% in both school-age children (4.5–17 years) and adults (18–45), whereas PPV for pre-schoolers was 68%. The PPV for doctor-diagnosed acute bronchitis/bronchiolitis in pre-schoolers was 26%, whereas a PPV of less than 1% was seen for COPD/chronic bronchitis independent of age group. Together, the PPV for a diagnosis of asthma, acute bronchitis/bronchiolitis and chronic bronchitis/COPD match up to 94% in pre-school children, 93% in school-age children and 97% in adults, respectively. The remaining 3–7%, correspond to individuals that have been given asthma medication for upper respiratory tract infections. Among pre-school children without an asthma diagnosis recorded in any medical record ($n = 166$), approximately 38% had been given a diagnosis of acute bronchitis/bronchiolitis by their physicians. Corresponding number in school-age children was 14% (9 of 66). Three adults had been given a COPD diagnosis at one consultation, but all three had also been given a diagnosis of asthma at other occasions (not tabulated).

Table 3 also shows PPV based on the asthma criteria by the Swedish Paediatric Society, assessed by combined information from all retrieved medical records for each

Table 1. Period prevalence (year 2008) of anti-asthmatic/eczema medication* in children and adults 0–45 years of age. Number of individuals in each age group in the Swedish population was retrieved from Statistics Sweden†

	Age group		
	0–4.5	>4.5–17	18–45
Asthma (R03)			
Total number of individuals	36 351	84 398	160 044
Sex (n, %)			
Male			
Female			
Total number of filled prescriptions for drugs for obstructive airway disease during 2008 ‡			
1 dispensed item	22 476 (61.8)	48 430 (57.4)	68 305 (42.7)
2 dispensed items	13 875 (38.2)	35 968 (42.6)	91 739 (57.3)
3 dispensed items	133 559	252 822	499 705
≥4 dispensed items	7508 (20.7)	28 089 (33.3)	61 270 (38.3)
Number of individuals in Sweden 2008† Male; Female	11 650 (32.1)	24 138 (28.6)	37 742 (23.6)
Prevalence (%) Male; Female	3945 (10.9)	9297 (11.0)	16 255 (10.2)
Any drug for obstructive airway diseases	13 248 (36.4)	22 874 (27.1)	46 546 (28.8)
Inhalations of selective β2-adrenoreceptor agonists	249 052	671 340	1 744 498
Inhalation of corticosteroids	235 537	637 350	1 671 429
Leukotriene receptor antagonists			
Eczema (D07A, D11AH01, D11AH02)			
Total number of individuals	32 669	56 265	141 281
Sex (n, %)			
Male			
Female			
Total number of filled prescriptions of glucocorticoids for external use during 2008	18 090 (55.3)	27 764 (49.3)	58 881 (41.7)
Total number of filled prescriptions of topical immunosuppressants during 2008	14 682 (44.7)	28 501 (50.7)	82 400 (58.3)
Prevalence (%) Male; Female	54 192	88 922	238 333
Any glucocorticoids for external use	587	2545	5904
Glucocorticoids for external use, mild (1)			
Glucocorticoids for external use, moderate (2)			
Glucocorticoids for external use, potent (3)			
Glucocorticoids for external use, very potent (4)			
Tacrolimus			
Picemolimus			

†Selective β2-adrenoreceptor agonists for systemic use (R03C) excluded.

Table 2. Study base that fulfilled inclusion criteria (*N*) in each group and number of patients for whom medical records were requested and retrieved.

	Anti-asthmatic drugs in SPDR without asthma diagnosis in NPR			Eczema drugs in SPDR without eczema diagnosis in NPR		Asthma diagnosis NPR	
	1	2	3	4	5	6	
Group	0-4.5	>4.5-17	18-45	0-17	0-4.5	>4.5-17	
Age years	10 001	16 853	128 747	40 364	28 248	26 478	
Study base, <i>N</i>	600	600	350	350	350	350	
Number of patients for whom medical records were requested, <i>n</i>	—	—	—	—	336 (96.0)	331 (94.6)	
Number of patients with an asthma diagnosis in NPR with ≥ 1 filled prescription of asthma medication in SPDR, <i>n</i> (%)	—	—	—	—	216 (61.7)*	214 (61.1) [†]	
Number of patients with an asthma diagnosis in NPR fulfilling the inclusion criteria of asthma medication in SPDR, <i>n</i> (%)	—	—	—	—	306 (87.4)	289 (82.6)	
Number of patients for whom medical records were retrieved, <i>n</i> (%)	486 (81.0)	395 (65.8)	234 (66.9)	242 (69.1)			
Sex, <i>n</i> (%)							
Male	281 (57.8)	203 (51.4)	93 (39.7)	115 (47.5)	202 (66.0)	155 (53.6)	
Female	205 (42.2)	192 (48.6)	141 (60.3)	127 (52.5)	104 (34.0)	134 (46.4)	

*Fulfilled criteria of asthma medication as displayed in Figure 1 for group 1

[†]Fulfilled criteria of asthma medication as displayed in Figure 1 for group 2.

Table 3. Positive Predictive Value (PPV) and 95% confidence interval (CI) estimated as the proportion of individuals with asthma medication with a doctor-diagnosed asthma or asthma-like diagnoses. PPV and 95%CI estimated as the proportion of pre-schoolers and school-age children with asthma medication that fulfilled the criteria of asthma or asthma in combination with obstructive bronchitis according to criteria by the Swedish Paediatric Society.

Doctor diagnosis <i>n/N</i> ; PPV (95%CI); missing (<i>n</i>) [†]	Age (years)					
	0–4.5		>4.5–17		18–45	
Asthma (J45)	320/469	0.68 (0.64–0.72)	329/371	0.89 (0.85–0.92)	24	171/193
Acute bronchitis and bronchiolitis (J20/J21)	123/469	0.26 (0.22–0.30)	16/371	0.04 (0.02–0.07)	24	11/193
Chronic bronchitis and COPD (J42/J44)	1/469	0.002 (0.0001–0.01)	–	–	–	3/193
Diagnosis by criteria*						
<i>n/N</i> ; PPV (95%CI); missing (<i>n</i>) [†]						
Asthma	339/455	0.75 (0.70–0.78)	340/361	0.94 (0.91–0.96)	55	–
Asthma or obstructive bronchitis	415/478	0.87 (0.83–0.90)	–	–	–	–

*≥3 obstructive periods before 2 years and/or ≥1 obstructive period after 2 years and/or ≥1 obstructive period independent of age, where the child has eczema, food allergy, other allergies, or if the child does not get better between periods of respiratory tract infections. Children under 2 years of age with asthma-like symptoms during respiratory tract infections, but without symptoms between infections, were defined as suffering from obstructive bronchitis.

[†]Individuals for whom no information was available at all were excluded in the analysis of PPV.

individual. The pre-schoolers had a PPV of 75% for asthma, whereas school-age children (>4.5–17 years) had a PPV of 94%. When combining pre-schoolers defined as asthmatics with children defined as having obstructive bronchitis, PPV increased to 87%. Approximately 6% (31 of 486) of pre-school children and 9% (34 of 395) of school-age children had missing information on the indication of the prescription and were therefore excluded in the analysis of PPV. Corresponding number for missing information in adults was 19% (44 of 234). There was no difference in PPV by sex or number of prescriptions (≥ 2 or ≥ 3 within different periods) for any doctor diagnosis or diagnosis by criteria (not tabulated).

Of the pre-school children that did not fulfil the asthma criteria, 18% (84 of 455; after exclusion of individuals with missing information) were defined as having obstructive bronchitis by criteria and 7% (32 of 455) as having been given asthma medication for other reasons such as cough or upper respiratory tract infections. All school-age children that did not fulfil the asthma criteria (6%) had been given a prescription for other reasons (not tabulated).

Eczema medication as a proxy for eczema diagnosis

Table 4 shows PPV for the 'umbrella diagnosis' dermatitis and the sub-diagnoses eczema, seborrhoeic dermatitis and contact dermatitis found in medical records based on medication in the SPDR. A PPV of 82% was estimated for dermatitis, whereas PPV was estimated to be 45% for the specific diagnosis of eczema (L20). Approximately 7% (17 of 242) of the children included in the eczema medication validation were lacking information on the indication for the prescription.

Table 4. Positive Predictive Value (PPV) and 95% Confidence Interval (CI) estimated as the proportion of children 0–17 years of age with filled prescriptions of pharmaceuticals of topical glucocorticoids or immunosuppressants that were assessed as having a diagnosis of unspecific dermatitis and sub-diagnoses of dermatitis

	Age (years)	
	0–17	
Diagnosis	<i>n</i>	PPV (95%CI)
Dermatitis*	199	0.82 (0.77–0.87)
Eczema (L20)	108	0.45 (0.38–0.51)
Seborrhoeic dermatitis (L21)	17	0.07 (0.04–0.11)
Contact dermatitis (L25); allergic (L23) and non-allergic (L24)	7	0.03 (0.02–0.06)

*Includes all children who were reviewed as either having been given a diagnosis of unspecific dermatitis (L30.9) by their physician specifically or if having been assigned any of the other diagnosis under the 'umbrella diagnosis' of dermatitis, such as eczema, seborrhoeic dermatitis and contact dermatitis. Since all children with a sub-diagnosis of dermatitis are included in the group dermatitis, PPV for all groups together exceeds 100%.

Validation of asthma diagnoses in the NPR

In the validation of asthma diagnoses in children in the NPR, about 78% of the pre-schoolers (0–4.5 years) fulfilled the asthma criteria set by the Swedish Paediatric Society. The ones that did not fulfil the asthma criteria were almost all defined as suffering from obstructive bronchitis (21%). Eighty-nine percent of the pre-school children fulfilled the asthma criteria when restricting analyses to children that also fulfilled the inclusion criteria of asthma medication in the validation of the SPDR, compared with 57% among those without asthma medication. In school-age children (>4.5–17 years), almost everyone (99%) fulfilled the asthma criteria, and there was no difference for children with asthma medication (99%) or without medication (98%) (not tabulated).

DISCUSSION

Our results show relatively high PPVs for asthma in all age groups, which suggest that asthma medication reported in the SPDR can function as a suitable proxy for a doctor-diagnosed asthma, as well as for asthma by criteria according to the Swedish Paediatric Society. Furthermore, the quality of doctor-diagnosed asthma in the NPR can be considered high because almost 80% of pre-school children and all school-age children with asthma reported in the NPR fulfilled the asthma criteria set by the Swedish Paediatric Society. Our results bring new possibilities to study asthma predictors, risk and co-morbidities in all children and young adults in Sweden and support previous findings in association studies that have used asthma medication as an indicator for asthma^{20–23} and asthma diagnoses in the NPR.^{20,24}

Previous studies on asthma medication as a proxy for asthmatic disease^{12–17,19,29} have been restricted to small sample sizes,¹⁵ specific regions^{12,14,17} or used prescribed medications instead of filled prescriptions of medication.^{13,16} The novelty with this study is the population-based design, where randomly selected medical records on a national level have been reviewed both to assess doctor-diagnosed asthma and asthma by criteria. Concerns against asthma medication as a proxy for asthma have been that asthma medication is often prescribed to wheezing infants and the response to the drugs is used as a diagnostic tool for asthmatic symptoms.³⁰ It is likely that PPV for asthma would have been lower if we had included individuals with only one dispensed item of asthma medication. Therefore, we only included individuals with at least two records of prescribed asthma medication. Furthermore, we did not include selective β_2 -agonist for systemic use (R03C) with the

objective to avoid unspecific, acute upper respiratory tract infection symptoms in pre-school children.

In this first study to evaluate eczema medications as a proxy for a diagnosis of eczema, PPV for the 'umbrella diagnosis' of dermatitis was rather high. However, the PPV estimated for an eczema diagnosis specifically was quite low. This indicates that using eczema medication as proxy for eczema may induce misclassification, thereby underestimating true associations in aetiological studies and the proxy should be used with caution. The World Allergy Organization recommends that under the 'umbrella term' dermatitis, eczema should replace the intermediate term atopic eczema/dermatitis syndrome. Further classification into atopic eczema should only be made after determination of Immunoglobulin E, antibodies or skin prick testing.³¹ Review based on validated standardized definitions for eczema³² was impossible because of lacking information and we could only calculate PPV for all diagnoses under the umbrella term dermatitis and each sub-diagnosis separately.

This is the first study to show population-based data on the utilization of anti-asthmatic drugs in Swedish children. As expected, both the period prevalence and the estimated incidence of anti-asthmatic drug usage decreased with increasing age^{18,33} and were more common in males than in females among younger children, with a shift to female predominance in adolescence and adult life.^{29,34} The prescription prevalence of any anti-asthmatic medication in Sweden is comparable with previously published prevalence data in Sweden^{35,36} and Norway.²⁹ In a study by Bianchi *et al.* prevalence rate from prescription data was also found to be comparable with previously published country-specific data on asthma prevalence in Denmark, the Netherlands and Canada.³⁷ A peak of incidence in the waiting-time distribution graph each year starting around April–May, especially during the year of 2006, is believed to correspond to high birch-pollen counts in Sweden.²⁸ However, the peak was less prominent in pre-school children compared with school-age children and adults, which could reflect a larger proportion of transient early wheezers and non-atopic asthmatics in the youngest children.³⁸

So far, there are no studies to our knowledge that have shown population-based data on utilization of drugs to treat eczema. Questionnaire-based studies with parental reports of atopic eczema have a prevalence of approximately 20%.² This is a much higher number than the prescription prevalence for any investigated eczema medication in the present study. In Sweden, over-the-counter (OTC) drugs for treatment of eczema can be purchased, which are not included in the SPDR. It is possible that children with mild symptoms might have

either not been treated at all or have only used OTC drugs and are therefore not included in our data. Our measure is likely to have high specificity for studying dermatitis; however, for eczema, given the low PPV in combination with the low negative predicted value (due to eczema patients using either OTC medications or none at all), its value in aetiological studies is questionable.

The main strengths of this study include our nation-wide population-based study design and the randomly selected patients to be included in the review of their medical records. By using random sampling, we were able to decrease the risk of selection bias in terms of regional differences and socio-economic status affecting prescribing habits. The SPDR is population-based and provides complete data regardless of age, gender, prescribing physician and reimbursement status. Even though our study period is limited to the start of the SPDR in 2005, we were able to avoid influences of seasonal variance. Furthermore, the medical records in the medication validation of asthma were both reviewed in terms of doctor diagnosis of asthma and based on set criteria, by independent external reviewers and not the prescribing physician. There was a slight difference in PPV between a doctor diagnosis of asthma and asthma according to our criteria in the validation of asthma medication, which could be explained by the fact that we were able to combine information from several medical records, giving us the possibility to study the patient over time. Our values of PPV would probably have increased if we had access to medical records from other occasions than just for the consultation where a prescription was given, due to that asthma is a chronic disease and physicians might neither give the patient a diagnosis at each consultation nor prescribe medication at each visit where a diagnosis is given. The snap-shot study design can also explain why not all children with an asthma diagnosis in the NPR could be verified as asthmatics.

We were not able to estimate PPV for different phenotypes of asthma, which is one limitation of this study. Nevertheless, our results with a lower PPV for asthma in pre-schoolers could represent the widely recognized picture of young wheezers.³⁹ A diagnosis of asthma becomes more accurate with increasing age,³⁰ and while our predefined criteria for asthma is one of this study's strengths, it can also be questioned because it includes both children with infection-induced symptoms, some of which have signs of allergy, and a group of children with allergic asthma with varying prognosis.⁴⁰ However, the obstructive symptoms for infection-induced and allergic asthma are fairly similar. The SPDR may be suitable to studies on the combined phenotype asthma and/or obstructive bronchitis, as

PPV (0.68+0.26) will then be at the same level as in the other age groups. Even though obstructive bronchitis might not have the same aetiology as asthma, a review of prospective birth cohorts on long-term outcomes of early onset wheezers concluded that wheezing that begins in early life and persists beyond the third year generally continues into adulthood.³⁹ Another way of capturing asthmatics and not transient wheezers in pre-school children would be to only include those with a diagnosis in the NPR, who also have more than two dispensed items of asthma medication reported in the SPDR. On the other hand, we would then have a low sensitivity as we would miss children with an asthma diagnosis from the PHCC, which does not report to the NPR. It is also possible that differences between SPDR and NPR may capture different asthma phenotypes, as appeared in the Danish study by Hansen *et al.*⁵ If so, a non-overlap between the methods may be due to different abilities to identify phenotypes, in which case they should be treated either as separate outcomes or combined in future aetiological studies. The SPDR could most likely function on its own in aetiological studies for school-age children and adults, because PPV for asthma medication as a proxy for asthma was high in these age groups. On the other hand, with access to patient register data, including these individuals would improve the sensitivity, without negative effects on PPV.

With our study design, we were not able to evaluate sensitivity and specificity of the use of asthma medication as a proxy for asthma. This would require a study design with medical evaluations of a random selection of the Swedish population and register information on these individuals. Our results will therefore not be useful in disease prevalence studies and cannot replace prospective cohort studies. PPV on the other hand, which measures the proportion of individuals identified as asthmatics by our proxy that have the disease, is useful for aetiological studies to assure that the outcome measure captures the true asthmatics. Prevalence estimates from cohort studies are also important, in combination with the prevalence of our proxy, to get a rough estimate of the negative predictive value, that is the proportion of individuals classified as non-asthmatic, but are truly non-asthmatic.

The objective behind defining the youngest age group to 0–4.5 years of age was that this was the only group for whom all filled prescriptions of asthma and eczema medication from birth would be captured in the register, as they were born after the initiation of the SPDR. The reason for including adults in the asthma validation was to find a validated measure that can be used to assess family history of asthma for

children. In the adult population, less than 2% had been given a diagnosis of COPD by their physicians, which corresponds to previously reported prevalence of COPD in young adults in the European Community Respiratory Health Survey.⁴¹ We cannot dismiss the fact that the adults, for whom an indication for a prescription was missing, did not suffer from COPD. However, by excluding adults above 45 years of age, the risk that COPD has biased our results is diminished.

Population-based registers are an excellent source of information for epidemiological studies;⁴² however, they are limited to a few selected countries. Because our results are based on the registers covering the Swedish population, the generalizability to other countries can further be questioned. The results are nevertheless important for the evaluation of study results from register-based epidemiological studies from these countries, which usually are relevant for a larger community.

In conclusion, our study suggests that asthma medication in the SPDR can be used as proxy for asthma, but not for eczema. This validation study of two Swedish registers opens for future large nation-wide register-based studies on asthma.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

KEY POINTS

- The population-based Swedish Prescribed Drug Register (SPDR) and National Patient Register (NPR) are excellent sources of information for epidemiological association studies.
- Asthma medication reported in the SPDR is a suitable proxy for asthma in both children and adults, but the same approach is insufficient for eczema.
- The quality of asthma diagnoses in the NPR can be considered high because approximately all school-age children fulfilled predefined criteria of asthma.

ACKNOWLEDGMENTS

First, we direct our great appreciation to Gerd Agerberg who has contributed with excellent data collection and management. We also want to direct our thanks to Professor Carl-Fredrik Wahlgren, Professor Pär Sparén and Dr Maria Böhme for fruitful discussions. Financial support was provided through the regional agreement

on medical training and clinical research (ALF) between Stockholm County Council and Karolinska Institutet, grants from the Swedish Research Council (grant numbers 80748301 and 2011-3060) and the Strategic Research Program in Epidemiology at Karolinska Institutet. C. A. was granted the ERS Romain Pauwel Research Award in 2011.

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