

Incidence rates of atopic dermatitis, asthma, and allergic rhinoconjunctivitis in Danish and Swedish children

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Background: Several studies have shown that the prevalence of the frequent chronic conditions of atopic dermatitis, asthma, and allergy has increased substantially for reasons not fully understood. Atopic diseases affect quality of life in both children and their family members.

Objective: Using national registers, we sought to establish up-to-date incidence rates of atopic dermatitis, asthma, and allergic rhinoconjunctivitis in the Danish and Swedish child populations.

Methods: Children born in Denmark from 1997 to 2011 or born in Sweden from 2006 to 2010 participated in this cross-national, population-based cohort study. Incidence rates of atopic dermatitis, asthma, and allergic rhinoconjunctivitis in the Danish and Swedish child cohorts were ascertained through disease-specific dispensed prescribed medication, specific hospital contacts, or both.

Results: In both countries the incidence rate of atopic dermatitis was stable during the study periods. The incidence rate of asthma increased until 2006 and stabilized for the rest of the study period in Denmark and increased in Sweden. The incidence rate of allergic rhinoconjunctivitis decreased in both countries.

Conclusion: The study revealed similar trends, with stable incidence rates of atopic dermatitis in both Danish and Swedish children, an increase and then stabilization in asthma incidence rates in Denmark and an increase in Sweden, and a decrease in allergic rhinoconjunctivitis incidence rates. At age 5 years, one third of all children were affected with at least one of the conditions

of atopic dermatitis, asthma, or allergic rhinoconjunctivitis. (*J Allergy Clin Immunol* 2015;■■■■:■■■-■■■.)

Key words: Atopy, children, incidence rate, pharmacoepidemiology

Studies have shown that the prevalence of atopic dermatitis, asthma, and allergy in Europe has increased substantially.¹⁻⁴ The reasons for the increase are not fully understood. Changes in medical practice and increased awareness of allergic diseases might play a role, as well as undefined changes in environmental exposures.⁵ Also, host factors, such as genetic factors⁶ and possible immune imbalance,⁷ are of importance. Atopic diseases affect quality of life in children; they receive more medication and have more visits to the family physician and hospital than other children.⁸ Thus the drugs most frequently used by Danish⁹ and Swedish¹⁰ children are asthma medications.

The Nordic countries have a long history of excellent national health registers. Data can be linked on an individual level by using a unique personal identifier, the Central Person Registration number (CPR),¹¹ which serves as a key reference to ensure accurate subject-level linkage between all national registers and making national cohort studies feasible. Also, national information on the use of dispensed prescribed medication has become available on an individual level in both Denmark and Sweden.^{12,13} Therefore it is possible to use information on specific drugs prescribed outside the hospital in nationwide cohort studies.

Prescribed medications to identify children with asthma through data from national registers have been used in previous studies.^{14,15} The prevalence of asthma in children and adolescents has been estimated by using information on prescribed medication and hospital diagnoses.¹⁶ One study used data from the Swedish Prescribed Drug Register to examine and validate the use of prescribed medication to identify asthma and eczema in Swedish children.¹⁷ To our knowledge, there are no studies reporting use of prescribed medication to define allergic rhinoconjunctivitis, and no prior studies have examined the pattern in incidence rates of the 3 atopic diseases in the entire child population in 2 separate countries.

Consequently, the aim of this study was to describe up-to-date trends in the incidence rates of atopic dermatitis, asthma, and allergic rhinoconjunctivitis in the Danish and Swedish child populations based on information on both inpatient and outpatient hospitalizations in combination with information on disease-specific dispensed prescribed medication.

METHODS

Study population

A cross-national cohort study was carried out using data from children born in Denmark and Sweden. The study population consisted of 972,836 live-born

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Supported by the Dagmar Marshalls Foundation and the Danish Lung Association. The funders played no role in the study design, data collection, analysis, interpretation, writing of the manuscript, or decision to submit the article for publication.

Disclosure of potential conflict of interest: This study was funded by the Dagmar Marshalls Foundation and the Danish Lung Association and based on work developed from a study originally commissioned by AbbVie. L. Henriksen's group has received funding from AbbVie, although AbbVie was not involved in this study. M. Linder's institution has received funding from AbbVie, Amgen, Bayer, Pfizer, Astellas, Otsuka, AstraZeneca, Takeda, and Novartis. H. Kieler's institution has received funding from AbbVie. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication April 22, 2014; revised January 26, 2015; accepted for publication February 4, 2015.

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0091-6749/\$36.00

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<http://dx.doi.org/10.1016/j.jaci.2015.02.003>

Abbreviations used

ATC: Anatomical Therapeutic Chemical classification system
 CPR: Central Person Registration number
 ICD-10: International Classification of Disease, version 10
 IRR: Incidence rate ratio
 NPR: Danish National Patient Register
 SPR: Swedish Patient Register

Danish children born from 1997 to 2011 and 534,541 Swedish children born from, 2006 to 2010 (Table 1). In Denmark the registration of prescribed medication by CPR started in 1995. However, until 1996, medication for Danish children was often prescribed and recorded by using the parents' CPRs, and therefore Danish children born from 1997 to 2011 were included in this study. In Sweden the registration of individually prescribed medication started July 1, 2005, and prescribed medication for children was recorded by using the child's CPR from the beginning. We included Swedish children born from January 1, 2006, to December 31, 2010.

Ethics

The study was approved by the Danish Data Protection Board (no. 2010-41-5166) and by the Regional Ethics Board in Stockholm (no. 2011/1064-31/4 and 2012/862-32). Register-based studies do not require approval from ethics committees in Denmark.

Registers

The Danish Medical Birth Register¹⁸ and the Swedish Medical Birth Register¹⁹ contain information on all births and newborns. From the Danish Medical Birth Register, we identified all children born live in Denmark throughout the study period. From the Swedish Medical Birth Register, we identified all children born live in Sweden throughout the study period.

The Danish National Patient Register (NPR)²⁰ and the Swedish Patient Register (SPR)²¹ contain information on all inpatient and outpatient and emergency department visits. From the NPR, we obtained diagnostic codes from 1997 to 2012, and from the SPR, we obtained diagnostic codes from 2006 to 2011. From the NPR and SPR, we used disease-specific International Classification of Disease, version 10 (ICD-10), diagnostic codes to identify children, both inpatients and outpatients, with atopic dermatitis, asthma, and allergic rhinoconjunctivitis.

The Danish National Prescription Registry¹² and the Swedish Prescribed Drug Register¹³ contain information on all dispensed prescribed medication classified according to the Anatomical Therapeutic Chemical classification system (ATC).²² From the Danish National Prescription Registry, we obtained data on dispensed prescribed medication from 1997 to 2012, and from Swedish Prescribed Drug Register, we obtained data on dispensed prescribed medication from 2006 to 2011.

Outcome definition

We identified children with atopic dermatitis, asthma, or allergic rhinoconjunctivitis using the disease-specific ICD-10 diagnostic codes from child hospital contacts (inpatient and outpatient hospitalizations). To increase the study sensitivity and identify children with atopic dermatitis, asthma, and allergic rhinoconjunctivitis followed by the general practitioner, we further included children who received specific medication for atopic dermatitis, asthma, or allergic rhinoconjunctivitis by dispensed prescriptions using the ATC codes for these medications. Therefore the 3 algorithms that were developed to define children with atopic dermatitis, asthma, or allergic rhinoconjunctivitis were based on disease-specific medication, specific hospital contacts, or both for the 3 atopic diseases.

The study group that developed the algorithms included specialists in dermatology, allergology, pharmacoepidemiology, and biostatistics. Furthermore,

a pediatric otorhinolaryngologist was consulted regarding the algorithm for allergic rhinoconjunctivitis.

Each algorithm was generated in 3 steps:

1. selection of disease-specific hospital diagnoses and disease-specific medication;
2. application of criteria of repetition of the disease-specific medication within 12 months because all 3 conditions are characterized by chronicity and recurrence; and
3. exclusion of other medical conditions known to lead to use of the medication types used as inclusion criteria in step 1.

The 3 outcome diseases were defined separately, and therefore each child could be affected by more than 1 of the 3 atopic diseases. The algorithms based on hospital contacts, disease-specific dispensed prescribed medications, or both are presented in Appendix E1 in this article's Online Repository at www.jacionline.org.

Statistical methods

Study periods. For simplicity and comparability between countries, 2006 was chosen as the reference year for both Denmark and Sweden.

Choice of follow-up was done separately for each country. The follow-up of the Danish cohort was chosen to be January 1, 1998, to December 31, 2011. Although medication should have been registered with the child's CPR already from 1997, it was not uncommon in 1997 that medication for small children was prescribed by using one of the parents' CPRs. From 1998, the number of prescriptions recorded by using maternal/paternal CPRs to small children and infants was negligible (author's data, available on request). The study period in Sweden was chosen to be January 1, 2006, until December 31, 2010. Because the algorithms included information on medication used twice within 12 months, the time period of 12 months of data collection after each year under study was obligatory. Thus to fulfill the criteria of the algorithms, the periods of data collection included 1 more year, 2012 in Denmark and 2011 in Sweden, than did the study periods.

Disease debut. Date of disease debut was defined as the first date of either a specific hospital diagnosis or the first date of a dispensed prescription of specific medication.

Descriptive statistics. Crude estimates of incidence rates for atopic dermatitis, asthma, and allergic rhinoconjunctivitis were presented by sex, age, and birth year in the Danish and Swedish child populations. Numbers of events for atopic dermatitis, asthma, and allergic rhinoconjunctivitis were presented by country, age group, birth year, and sex. Furthermore, incidence rates of atopic dermatitis, asthma, and allergic rhinoconjunctivitis were presented by season.

Statistical modeling. In this cohort study design the age composition of the study cohort changed over study calendar time. In the beginning of the study period, the cohorts consisted of only infants, whereas later the cohort also consisted of older children. We accounted for this in the Cox regression model by using age as the underlying time scale. Using age as the underlying time scale ensured that only children of similar age were compared when the calendar time effect was estimated. In the model we assumed that the age effect was similar during all study years (no interaction between age and calendar time).

To take account of a possible sex effect, we stratified the baseline hazard on sex, where the calendar effect was assumed to be similar between sexes. Separate Cox proportional hazard models were used to calculate the incidence rate ratio (IRR) of atopic dermatitis, asthma, and allergic rhinoconjunctivitis between calendar years. To do this, we assumed that the calendar effect on the IRR was piecewise constant, with jumps at January 1 of each year.

The children were followed from the day of birth until the onset of outcome, emigration, death, or end of follow-up, whichever came first. The end of follow-up was December 31, 2011, in Denmark and December 31, 2010, in Sweden.

Identifying the period effect when age and cohort effects were present. When age was used as the underlying time axis, it was not possible to identify the period effect when the estimates were adjusted for a possible cohort effect in the naive way. However, by using the

TABLE I. Number of children in the total Danish population born from 1997 to 2011 and in the total Swedish population born from 2006 to 2010 and by sex

	Denmark, no. (%)	Sweden, no. (%)
Total	972,836 (100%)	534,541 (100%)
Girls	474,174 (48.7%)	259,642 (48.6%)
Boys	498,662 (51.3%)	274,899 (51.4%)

principle described by Carstensen,²³ it was possible to identify a period effect and have age as the underlying time axis and adjust for a detrended cohort effect. Thereby we assumed that there was no trend in the cohort effect, although the cohort effect was allowed to have fluctuations without any trend.

Seasonality. We examined the seasonal effect on the risk of atopic dermatitis, asthma, and allergic rhinoconjunctivitis. In this analysis we divided each year into 4 seasons: winter (December-February), spring (March-May), summer (June-August), and autumn (September-November). The season during which the risk was assumed to be the lowest was chosen as the reference season. For atopic dermatitis and asthma, summer was chosen as the reference season, and for allergic rhinoconjunctivitis, winter was chosen as the reference season. When the effect of calendar year was estimated, we stratified on the season of birth. This had practically the same effect as adjusting for season because age was used as underlying time axis. The children were compared with other children with the exact same age and same season of birth, and therefore the running season was similar.

All analyses were carried out with SAS software (version 9.3; SAS, Cary, NC).

RESULTS

Atopic dermatitis

On the basis of information on disease-specific dispensed prescribed medication, specific hospital contacts, or both, we found that the majority of children had a debut of atopic dermatitis in infancy. In both Denmark and Sweden boys were more often identified with atopic dermatitis than girls (Table II), and the risk of atopic dermatitis was high during winter and spring (December-May, Table III).

Time trends in the IRR of atopic dermatitis

Throughout the study periods, when using disease-specific dispensed prescribed medication, specific hospital contacts, or both, the incidence rate of atopic dermatitis was stable among Danish children, ranging from an IRR of 1.05 (95% CI, 1.01-1.08) in 1998 to an IRR of 1.06 (95% CI, 1.03-1.09) in 2011, and in Swedish children, ranging from an IRR of 1.05 (95% CI, 1.00-1.10) in 2007 to an IRR of 0.99 (95% CI, 0.95-1.03) in 2010 (Fig 1).

Looking at atopic dermatitis hospital diagnoses only, incidence rates were stable in both countries (see Table E1 and Table E2 in this article's Online Repository at www.jacionline.org).

Asthma

The incidence rate of asthma peaked between 1 and 2 years of age (Table II). In both Denmark and Sweden boys were more often affected with asthma. In Denmark the risk of asthma was high during autumn and winter (September-February), and in Sweden the risk of asthma was high during winter and spring (December-May, Table III).

Time trend in the IRR of asthma

Based on information on disease-specific dispensed prescribed medication, specific hospital contacts, or both, the incidence rate of asthma increased in the Danish child population, ranging from an IRR of 0.65 (95% CI, 0.61-0.67) in 1998 to an IRR of 0.71 (95% CI, 0.67-0.73) in 2011, and in the Swedish child population, ranging from an IRR of 1.08 (95% CI, 1.03-1.14) in 2007 to an IRR of 1.25 (95% CI, 1.21-1.30) in 2010 (Fig 1). For the Danish child population, the incidence rate of asthma peaked in 2006 but decreased again after that time point. The incidence rate of asthma hospitalizations in Danish children was stable throughout the study period (see Table E1), whereas the incidence rate of asthma hospitalizations in Swedish children increased throughout the study period (see Table E2).

Allergic rhinoconjunctivitis

Based on information on hospital contacts, disease-specific prescribed medication, or both, the incidence rates of allergic rhinoconjunctivitis peaked between 1 and 2 years of age. In both the Danish and Swedish child populations, boys were more often affected than girls (Table II). The risk of allergic rhinoconjunctivitis peaked during spring and summer (March-August) in both Denmark and Sweden (Table III).

Time trend in the IRR of allergic rhinoconjunctivitis

Based on information on disease-specific prescribed medication, specific hospital contacts, or both, the incidence rates of allergic rhinoconjunctivitis decreased in the Danish child population, ranging from an IRR of 1.17 (95% CI, 1.12-1.23) in 1998 to an IRR of 0.78 (95% CI, 0.75-0.80) in 2011, and in the Swedish child population, ranging from an IRR of 0.96 (95% CI, 0.87-1.05) in 2007 to an IRR of 0.62 (95% CI, 0.55-0.66) in 2010 (Fig 1). The decrease was based on a reduction in medication use only because the incidence rate of allergic rhinoconjunctivitis hospitalizations was stable during the study period (see Tables E1 and E2).

Lifetime prevalences

Using hospital contacts, disease-specific dispensed prescribed medications, or both, the lifetime prevalence of atopic dermatitis at age 5 years was 13% in Danish and 10% in Swedish children. The lifetime prevalence of asthma at age 5 years was 12% in Danish and 16% in Swedish children. The lifetime prevalence at age 5 years of allergic rhinoconjunctivitis was 7% in Danish and 11% in Swedish children (Table IV). Thus at age 5 years, approximately one third of the child population in Denmark and Sweden was or had been affected with at least 1 of the 3 atopic conditions (Table IV).

Model control

We plotted observed rates versus age by period and cohort and also observed rates versus cohort and versus period by age (these plots are available upon request).²³ Because the lines in these plots are very close to being parallel, we found that the calendar effect was almost constant over age, meaning that we had no reason to believe the proportional hazard assumption was not fulfilled. Further on, the martingale residuals, which were used to examine the model fit, showed no sign of violation of model assumptions (figures not shown).²⁴

TABLE II. Events per 10,000 person years of atopic dermatitis, asthma, and allergic rhinoconjunctivitis based on information on hospital contact, disease-specific prescribed medication, or both by age and sex in Danish children born from 1997 to 2011 and Swedish children born from 2006 to 2010

	Atopic dermatitis			Asthma			Allergic rhinoconjunctivitis		
	Person years/1,000	Events	Crude rate: Events per 10,000 person years	Person years/1,000	Events	Crude rate: Events per 10,000 person years	Person years/1,000	Events	Crude rate: Events per 10,000 person years
Denmark (n = 972,836) total	6,375	137,090	215	6,557	113,189	173	6,686	104,363	156
Age (y)									
0	882	46,033	522	894	34,941	391	903	7,184	80
1	811	35,223	434	818	38,701	473	859	15,861	185
2-4	1,968	32,662	166	2,006	25,185	126	2,113	35,816	169
5-9	2,045	17,892	87	2,129	11,233	53	2,143	35,535	166
10-15	667	5,280	79	709	3,129	44	667	9,967	149
Sex									
Female	3,128	64,430	206	3,266	44,247	135	3,297	43,267	131
Male	3,247	72,660	224	3,290	68,942	209	3,388	61,096	180
Sweden (n = 582,536) total	1,242	38,022	306	1,222	53,073	434	1,265	20,219	231
Age (y)									
0	468	21,179	452	469	21,899	466	476	6,785	143
1	345	10,646	308	340	20,002	587	356	11,553	324
2-4	428	6,197	145	411	11,172	271	432	10,881	251
Sex									
Female	608	16,234	267	604	20,220	334	617	12,338	200
Male	633	21,788	344	618	32,853	531	647	16,881	261

TABLE III. Risk of atopic dermatitis, asthma, or allergic rhinoconjunctivitis with 95% CIs based on information on hospital contact, disease-specific prescribed medication, or both by season for Danish children born from 1997 to 2011 and Swedish children born from 2006 to 2010

Season	Atopic dermatitis			Asthma			Allergic rhinoconjunctivitis		
	Person years/1,000	Events	IRR (95% CI)	Person years/1,000	Events	IRR (95% CI)	Person years/1,000	Events	IRR (95% CI)
Denmark									
Winter*	1,551	36,143	1.25 (1.23-1.27)	1,594	35,649	2.24 (2.20-2.29)	1,627	15,565	Reference
Spring†	1,564	40,050	1.40 (1.35-1.39)	1,608	27,767	1.72 (1.69-1.75)	1,644	29,904	1.90 (1.86-1.94)
Summer‡	1,613	29,753	Reference	1,660	16,386	Reference	1,691	41,827	2.57 (2.52-2.62)
Autumn§	1,645	31,145	1.03 (1.02-1.05)	1,694	33,387	2.03 (1.99-2.07)	1,723	17,067	1.03 (1.01-1.05)
Sweden									
Winter*	345	11,509	1.41 (1.37-1.45)	319	17,535	2.18 (2.12-2.23)	351	6,586	Reference
Spring†	342	12,531	1.55 (1.51-1.59)	336	18,413	2.31 (2.25-2.36)	348	11,158	1.74 (1.68-1.79)
Summer‡	375	8,738	Reference	368	8,533	Reference	381	10,787	1.52 (1.47-1.56)
Autumn§	402	10,370	1.13 (1.10-1.17)	395	15,695	1.73 (1.70-1.78)	408	6,770	0.87 (0.84-0.90)

*Winter was defined as December, January, and February.

†Spring was defined as March, April, and May.

‡Summer was defined as June, July, and August.

§Autumn was defined as September, October, and November.

||The reference group was chosen according to clinical symptomatology of atopic dermatitis, asthma, and allergic rhinoconjunctivitis.

DISCUSSION

According to information on disease-specific dispensed prescribed medication, specific hospital contacts, or both, the incidence rate of atopic dermatitis was stable in Denmark and Sweden. In Denmark the incidence rate of asthma peaked in 2006 and decreased afterward, and the incidence rate of asthma increased in Sweden during the study period. The incidence rate of allergic rhinoconjunctivitis decreased in both countries. For all 3 diseases, the incidence rates of hospital contacts were stable during the study periods, and therefore the changes observed in the incidence rates could mainly be explained by changes in specific medication use. Because the incidence rates of

atopic dermatitis based on information on disease-specific dispensed prescribed medication, specific hospital contacts, or both was stable while the incidence rate of asthma was increasing and the incidence rate of allergic rhinoconjunctivitis was decreasing, the trends cannot be explained readily by increased professional and public awareness of allergy and allergens.

Overall, atopic dermatitis, asthma, and allergic rhinoconjunctivitis were common among children in Denmark and Sweden, affecting nearly one third of the children at 5 years of age.

To our knowledge, no prior studies examined the incidence rates of atopic diseases in children at a population-based level in 2 separate countries using information on disease-specific

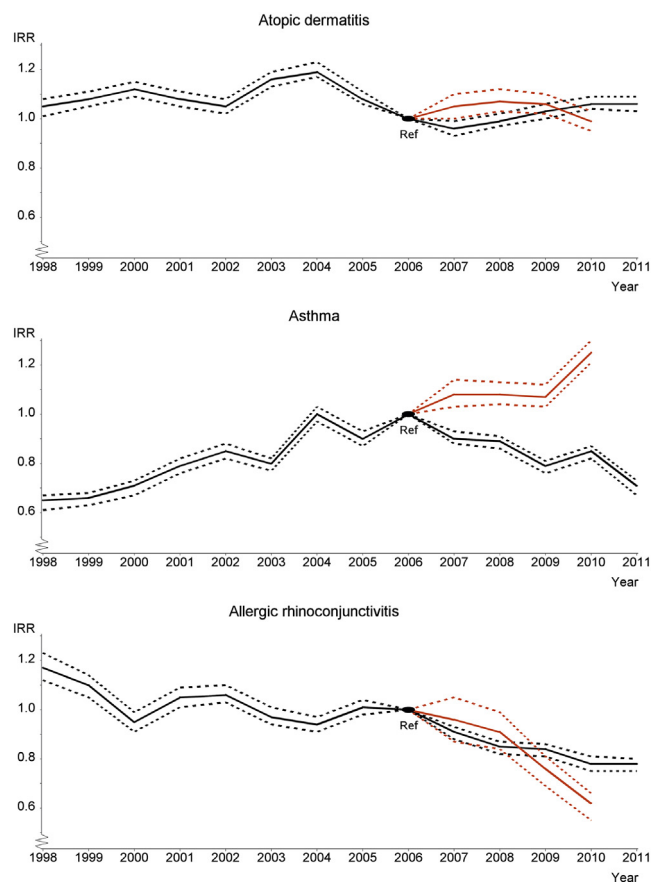


FIG 1. IRRs and 95% CIs of atopic dermatitis, asthma, and allergic rhinoconjunctivitis using 2006 as the reference year based on information on hospital contacts, disease-specific prescribed medication, or both in Danish children born from 1997 to 2011 (black line) and in Swedish children born from 2006 to 2010 (red line).

dispensed prescribed medication, specific hospital contacts, or both.

Atopic dermatitis

In 2 Danish studies Olesen et al²⁵ observed that the cumulative incidence of atopic dermatitis stabilized from 1993 to 1998, and Stensen et al²⁶ found the prevalence of atopic dermatitis from 1986 to 2001 to be increasing. Using data from Denmark and Sweden, we found no signs of change in the incidence of atopic dermatitis during more recent years. As expected, children in both Denmark and Sweden had their debut of atopic dermatitis in infancy. Although prior studies show that the pattern in sex distribution among patients with atopic dermatitis depended, among other factors, on age, nationality, and setting, it was no surprise that we identified more boys than girls with atopic dermatitis.²⁷ As expected, we found that children more often experienced atopic dermatitis during winter and spring (December-May).²⁸

Asthma

The finding in Denmark of a stabilization in the incidence rate of asthma in 2006 followed by a decrease based on information on hospital contacts, disease-specific dispensed prescribed medication, or both might indicate a positive effect of the antismoking

legislation implemented in Denmark in 2007, as seen in prior studies from England and Canada.^{29,30} In Sweden the antismoking legislation was implemented in 2005 and parents of infants appear to smoke less during the 2000s.³¹

Furthermore, changes in diagnostic and prescription practices might partly explain the changes in time trends of the incidence rate of asthma. For example, in the beginning of the study period, the use of inhaled corticosteroids was thought by clinicians to actually change the course of asthma in the direction of milder disease and less loss of lung function, whereas later in the study period, guidelines revealed that the use of inhaled corticosteroids most likely controlled asthma disease and symptoms but did not change the course of the disease.³²

Day care attendance has been related to an increased risk of viral airway infections in early childhood.³³ Children in Denmark and Sweden generally start day care at around 1 year of age. Start in day care attendance probably explains why the incidence rate of asthma peaked between 1 and 2 years of age. It is noteworthy that the majority of asthma diagnosed in the present study in infancy and early childhood most likely is early wheezing, with winter exacerbations explained by frequent viral airway infections that might not necessarily lead to chronic asthma disease also in later childhood and adolescence. In good accordance with prior knowledge, we identified most boys with asthma, and asthma incidence peaked during winter and spring (December-May).³⁴

Allergic rhinoconjunctivitis

The incidence rates of allergic rhinoconjunctivitis in both Denmark and Sweden decreased during the study periods of 15 years in Denmark and 5 years in Sweden based on information on disease-specific dispensed prescribed medication, specific hospital contacts, or both. Prior studies examined the trend in the prevalence of allergic rhinoconjunctivitis with diverging results.^{4,35} However, no prior studies examined the time trend of the incidence rate of allergic rhinoconjunctivitis already from birth using information on hospital diagnoses, probably representing more severe disease in addition to information on use of specific prescribed medication representing mild-to-moderate disease.

We observed that some children experienced the debut of allergic rhinoconjunctivitis already in infancy. In the development of the algorithm to define allergic rhinoconjunctivitis, we excluded children using antihistamines who had hospital diagnoses of other diseases than allergic rhinoconjunctivitis; however, the majority of children using antihistamines did not have a hospital diagnosis of other disease, and therefore the specificity of our diagnosis of allergic rhinoconjunctivitis might still be decreased by antihistamine use because of allergic conditions other than allergic rhinoconjunctivitis. As expected, we found that boys were more often affected with allergic rhinoconjunctivitis and that allergic rhinoconjunctivitis peaked during spring and summertime (March-August).^{28,34}

Strengths

Because of the use of a unique identification number, which is given at birth or immigration and kept throughout life for each subject in our populations, and a long history of national health registers in Scandinavian countries, we have the ability to perform

TABLE IV. Lifetime prevalence of children with atopic dermatitis, asthma, allergic rhinoconjunctivitis, and any atopic disease in the Danish population born from 1997 to 2011 and in the Swedish population born from 2006 to 2010 based on hospital contact, disease-specific prescribed medication, or both

Prevalence Age (y)	Atopic dermatitis (%)		Asthma (%)		Allergic rhinoconjunctivitis (%)		Any atopic dermatitis, asthma or allergic rhinoconjunctivitis (%)	
	Denmark	Sweden	Denmark	Sweden	Denmark	Sweden	Denmark	Sweden
1	5.1	4.4	3.9	4.7	0.7	1.5	9.3	9.5
2	9.1	7.3	8.2	10.1	2.6	4.6	17.9	18.5
3	11.2	8.9	9.8	13.0	4.3	7.1	21.9	23.4
4	12.4	9.8	10.8	14.6	5.8	9.2	24.6	26.4
5	13.4	10.5	11.5	15.9	7.4	10.7	26.8	28.7
6	14.2	—	12.1	—	8.9	—	28.6	—
7	15.0	—	12.5	—	10.4	—	30.4	—
8	15.7	—	13.0	—	11.9	—	32.1	—
9	16.4	—	13.4	—	13.3	—	33.7	—
10	17.0	—	13.8	—	14.8	—	35.3	—
11	17.7	—	14.2	—	16.1	—	36.8	—
12	18.3	—	14.6	—	17.4	—	38.2	—
13	18.9	—	15.0	—	18.5	—	39.5	—
14	19.6	—	15.3	—	19.5	—	40.7	—
15	20.4	—	15.6	—	20.4	—	41.9	—

large-scale epidemiologic studies. Thus the size of the national population-based cohorts included in this study is the major strength of the study. The algorithms we used to define atopic dermatitis, asthma, and allergic rhinoconjunctivitis consisted of information of clear relevance to the quality of life of the children and families and of clinical relevance being based on physicians' considerations, diagnosis and management, and repeated prescriptions of disease-specific medication. In the process of developing our algorithms, we collaborated with specialists in allergic diseases to identify the specific disease patterns in hospital admissions and repeated numbers of dispensed prescribed medication in children with atopic diseases. Prior studies, especially with asthma in focus, also used data on dispensed prescribed medication¹⁴ or dispensed prescribed medication in combination with questionnaires³⁶ administered to affected children and adolescents. None of these studies were cross-national studies on a population-based level using information on both specific hospital admissions and repeated use of specific prescribed medications to establish up-to-date incidence rates of atopic dermatitis, asthma, and allergic rhinoconjunctivitis among children.

Using data on disease-specific dispensed prescribed medication made it possible to identify and include patients with atopic dermatitis, asthma, and allergic rhinoconjunctivitis in primary care in both Denmark and Sweden. Although over-the-counter use of both antihistamines and corticosteroids exists in both Denmark and Sweden and might slightly decrease the sensitivity of our study, the specificity of the present study was secured by the fact that our measures of the incidence rates of atopic dermatitis, asthma, and allergic rhinoconjunctivitis were based on repeated decisions by the medical doctor who examined the children and prescribed medication.

By including information on prescribed medication, we expect the majority of the patient population from primary care was included, namely all patients treated with antiatopic medication.

Although the content and criteria of the algorithms used to define the outcome diseases in the present study might be further optimized, this would not change the resulting patterns presented as ratios over the study years.

Limitations

Because registration of the use of prescribed medication by using personal identification numbers in Sweden has only started recently, the birth cohorts of the present study consisted of rather young children. However, studies validating diagnostic coding from the NPR and the Swedish inpatient register showed high validity. This high validity cannot uncritically be applied to other diseases because it depends on the disease of interest.^{21,37}

Furthermore, our results are closely associated with outcome definitions and should therefore be interpreted with caution. However, use of incidence rates as outcome measures secured the robustness of the trends in disease development. Because no prior studies reported population-based incidence rates of atopic dermatitis, asthma, and allergic rhinoconjunctivitis using hospital contacts, disease-specific dispensed prescribed medications, or both, it was not possible to compare our results with those of other studies. However, the patterns identified for sex, seasonality, and age were in good accordance with prior knowledge.^{27,28,34}

Another limitation of this study was that the algorithms used to define atopic dermatitis, asthma, and allergic rhinoconjunctivitis have not yet been clinically validated. However, a recent Swedish study of a child population aged 4 to 17 years found that 99% of the children with registered use of antiasthma medication were in fact asthmatic, but a similar approach cannot be used as a proxy for eczema.¹⁷

Conclusion

The present study established up-to-date national population-based incidence rates of atopic diseases in young Scandinavian children, finding the incidence rate of atopic dermatitis to be stable, the incidence rate of asthma increasing in Sweden but decreasing in Denmark, and the incidence rate of allergic rhinoconjunctivitis to be decreasing. Furthermore, we found a similar pattern in the peaks of incidence rates for age groups, sex, and seasonality in both countries. In addition, we found approximately one third of children in Denmark and Sweden were or had been affected with at least 1 atopic condition at 5 years of age.

We thank Allan Linneberg, MD, PhD; Ingegård Anveden Berglind, MD, PhD; and Thomas Hjuler, MD, PhD, for their help and suggestions creating the algorithms used to identify both Danish and Swedish children affected by atopic dermatitis, asthma, and allergic rhinoconjunctivitis. Furthermore, we thank the reviewers for their good and appropriate comments.

Key messages

- Incidence rates of atopic dermatitis, asthma, and allergic rhinoconjunctivitis change over time in Denmark and Sweden, with no uniform picture.
- One third of the child populations were or had been affected by atopic disease at age 5 years.

REFERENCES

- Hansen TE, Evjenth B, Holt J. Increasing prevalence of asthma, allergic rhinoconjunctivitis and eczema among schoolchildren: three surveys during the period 1985-2008. *Acta Paediatr* 2013;102:47-52.
- McNeill G, Tagiyeva N, Aucott L, Russell G, Helms PJ. Changes in the prevalence of asthma, eczema and hay fever in pre-pubertal children: a 40-year perspective. *Paediatr Perinat Epidemiol* 2009;23:506-12.
- Schernhammer ES, Vutuc C, Waldhor T, Haidinger G. Time trends of the prevalence of asthma and allergic disease in Austrian children. *Pediatr Allergy Immunol* 2008;19:125-31.
- Grize L, Gassner M, Wuthrich B, Bringolf-Isler B, Takken-Sahli K, Sennhauser FH, et al. Trends in prevalence of asthma, allergic rhinitis and atopic dermatitis in 5-7-year old Swiss children from 1992 to 2001. *Allergy* 2006;61:556-62.
- Jarvis D, Chinn S, Luczynska C, Burney P. The association of family size with atopy and atopic disease. *Clin Exp Allergy* 1997;27:240-5.
- van Beijsterveldt CE, Boomsma DI. Genetics of parentally reported asthma, eczema and rhinitis in 5-yr-old twins. *Eur Respir J* 2007;29:516-21.
- Prescott S, Saffery R. The role of epigenetic dysregulation in the epidemic of allergic disease. *Clin Epigenetics* 2011;2:223-32.
- O'Connell EJ. The burden of atopy and asthma in children. *Allergy* 2004; 59(suppl 78):7-11.
- Danish Pharmacy. Lægemidler i Danmark 2012. Available at: http://www.apotekerforeningen.dk/om-apotekerne/regulering-af-apotekerne/~media/Apotekerforeningen/publikationer/Laegemidler_i_Danmark_2012.ashx. Accessed March 26, 2014.
- The National Board of Health and welfare. Prescribed Drug Register. Available at: <http://www.socialstyrelsen.se/register/halsodataregister/lakemedelsregistret>. Accessed March 26, 2014.
- Pedersen CB, Gotzsche H, Moller JO, Mortensen PB. The Danish Civil Registration System. A cohort of eight million persons. *Dan Med Bull* 2006;53:441-9.
- Kildemoes HW, Sorensen HT, Hallas J. The Danish National Prescription Registry. *Scand J Public Health* 2011;39(7 suppl):38-41.
- Wettermark B, Hammar N, Forde CM, Leimanis A, Otterblad OP, Bergman U, et al. The new Swedish Prescribed Drug Register—opportunities for pharmacoepidemiological research and experience from the first six months. *Pharmacoepidemiol Drug Saf* 2007;16:726-35.
- Furu K, Skurtveit S, Langhammer A, Nafstad P. Use of anti-asthmatic medications as a proxy for prevalence of asthma in children and adolescents in Norway: a nationwide prescription database analysis. *Eur J Clin Pharmacol* 2007;63:693-8.
- Moth G, Vedsted P, Schiotz P. Identification of asthmatic children using prescription data and diagnosis. *Eur J Clin Pharmacol* 2007;63:605-11.
- Hoffmann F, Glaeske G. Prescriptions as a proxy for asthma in children: a good choice? *Eur J Clin Pharmacol* 2010;66:307-13.
- Ortqvist AK, Lundholm C, Wettermark B, Ludvigsson JF, Ye W, Almqvist C. Validation of asthma and eczema in population-based Swedish drug and patient registers. *Pharmacoepidemiol Drug Saf* 2013;22:850-60.
- Knudsen LB, Olsen J. The Danish Medical Birth Registry. *Dan Med Bull* 1998;45: 320-3.
- Cnattingius S, Ericson A, Gunnarskog J, Kallen B. A quality study of a medical birth registry. *Scand J Soc Med* 1990;18:143-8.
- Mosbech J, Jorgensen J, Madsen M, Rostgaard K, Thornberg K, Poulsen TD. [The national patient registry. Evaluation of data quality]. *Ugeskr Laeger* 1995;157: 3741-5.
- Ludvigsson JF, Andersson E, Ekblom A, Feychting M, Kim JL, Reuterwall C, et al. External review and validation of the Swedish national inpatient register. *BMC Public Health* 2011;11:450.
- World Health Organization. Structure and principles. Available at: http://www.whocc.no/atc/structure_and_principles. Accessed March 18, 2014.
- Carstensen B. Age-period-cohort models for the Lexis diagram. *Stat Med* 2007;26: 3018-45.
- Lin DY, Wei LJ, Ying Z. Checking the Cox model with cumulative sums of martingale-based residuals. *Biometrika* 1993;80:557-72.
- Olesen AB, Bang K, Juul S, Thestrup-Pedersen K. Stable incidence of atopic dermatitis among children in Denmark during the 1990s. *Acta Derm Venereol* 2005;85:244-7.
- Stensen L, Thomsen SF, Backer V. Change in prevalence of atopic dermatitis between 1986 and 2001 among children. *Allergy Asthma Proc* 2008;29:392-6.
- Linneberg A, Simonsen JB, Petersen J, Stensballe LG, Benn CS. Differential effects of risk factors on infant wheeze and atopic dermatitis emphasize a different etiology. *J Allergy Clin Immunol* 2006;117:184-9.
- Cantani A. Pediatric allergy, asthma and immunology; chapter 5; Epidemiology and natural history of atopic disease; Springer-Verlag Berlin Heidelberg: 2008; pp 363-420.
- Millett C, Lee JT, Lavery AA, Glantz SA, Majeed A. Hospital admissions for childhood asthma after smoke-free legislation in England. *Pediatrics* 2013; 131:e495-501.
- Naiman A, Glazier RH, Moineddin R. Association of anti-smoking legislation with rates of hospital admission for cardiovascular and respiratory conditions. *CMAJ* 2010;182:761-7.
- Socialstyrelsen. Amning och föräldrars rökvanor. Available at: <http://www.socialstyrelsen.se/publikationer2014/2014-9-37>. Accessed September 24, 2013.
- Global strategy for asthma management and prevention in children 5 years and younger. Global Initiative for Asthma (GINA) 2009. Available at: <http://www.ginasthma.org/>. Accessed February 25, 2015.
- Hagerhed-Engman L, Bornehag CG, Sundell J, Aberg N. Day-care attendance and increased risk for respiratory and allergic symptoms in preschool age. *Allergy* 2006;61:447-53.
- Duggan EM, Sturley J, Fitzgerald AP, Perry IJ, Hourihane JO. The 2002-2007 trends of prevalence of asthma, allergic rhinitis and eczema in Irish schoolchildren. *Pediatr Allergy Immunol* 2012;23:464-71.
- Duksal F, Akcay A, Becerir T, Ergin A, Becerir C, Guler N. Rising trend of allergic rhinitis prevalence among Turkish schoolchildren. *Int J Pediatr Otorhinolaryngol* 2013;77:1434-9.
- Bechtold P, Ranzi A, Gambini M, Capelli O, Magrini N, Cavallini R, et al. Assessing paediatric asthma occurrence through dispensed prescription data and questionnaires. *Eur J Public Health* 2013;23:873-8.
- Mason K, Thygesen LC, Stenager E, Bronnum-Hansen H, Koch-Henriksen N. Evaluating the use and limitations of the Danish National Patient Register in register-based research using an example of multiple sclerosis. *Acta Neurol Scand* 2012;125:213-7.

TABLE E1. IRRs with 95% CIs of hospital contacts in Denmark because of atopic dermatitis, asthma, or allergic rhinoconjunctivitis (reference year 2006)

Year of hospitalization	Atopic dermatitis		Asthma		Allergic rhinoconjunctivitis	
	IRR	95% CI	IRR	95% CI	IRR	95% CI
1998	0.93	0.82-1.04	0.94	0.89-0.99	1.56	1.28-2.05
1999	1.10	1.01-1.22	0.96	0.92-1.01	1.22	0.97-1.57
2000	1.04	0.94-1.15	0.94	0.89-0.98	0.94	0.71-1.19
2001	1.13	1.04-1.25	1.02	0.98-1.06	1.09	0.90-1.32
2002	0.86	0.76-0.95	0.98	0.94-1.03	1.11	0.94-1.32
2003	0.88	0.78-0.97	0.92	0.88-0.96	1.03	0.87-1.20
2004	1.02	0.93-1.12	1.10	1.07-1.15	0.93	0.78-1.08
2005	1.09	1.00-1.19	0.95	0.91-0.99	1.00	0.87-1.15
2006	Reference	Reference	Reference	Reference	Reference	Reference
2007	0.82	0.73-0.91	0.91	0.87-0.95	0.98	0.86-1.11
2008	0.88	0.79-0.97	0.87	0.83-0.91	0.77	0.64-0.88
2009	1.01	0.92-1.11	0.86	0.82-0.89	1.06	0.94-1.20
2010	1.10	1.01-1.21	0.92	0.88-0.96	1.04	0.91-1.17
2011	1.16	1.07-1.27	0.85	0.81-0.89	1.27	1.14-1.44

TABLE E2. IRRs with 95% CIs of hospital contacts in Sweden because of atopic dermatitis, asthma, or allergic rhinoconjunctivitis (reference year 2006)

Year of hospitalization	Atopic dermatitis		Asthma		Allergic rhinoconjunctivitis	
	IRR	95% CI	IRR	95% CI	IRR	95% CI
2006	Reference	Reference	Reference	Reference	Reference	Reference
2007	1.12	1.04-1.20	1.03	0.96-1.10	1.09	0.78-1.48
2008	1.19	1.12-1.27	1.04	0.98-1.11	1.23	0.97-1.60
2009	1.33	1.27-1.42	1.08	1.03-1.14	1.24	1.00-1.58
2010	1.25	1.19-1.33	1.15	1.10-1.22	1.07	0.84-1.35

Supplemental, Appendix 1A

Algorithm to define children with atopic dermatitis

Children with atopic dermatitis fulfilled either criterion 1 – 3.

CRITERIA 1 (ICD-10):

≥1 hospital contact for:

L20 “atopic dermatitis”

L308C “winter feet”

CRITERIA 2 (based on ATC):

≥1 filled prescription of: D11AH “agents for dermatitis: tacrolimus, pimecrolimus” **without any of the exclusion criteria specified below**

CRITERIA 3 (based on ATC):

≥ 2 filled prescriptions of: D07 “corticosteroids for topical use” within 12 months **without any of the exclusion criteria specified below**

Without co-occurring hospital contacts and/ or combination of filled prescriptions below (exclusions criteria):

Children WITHOUT L20 “atopic dermatitis” with a diagnosis of: L21 “seborrhoeic dermatitis”, L22 “diaper dermatitis” L23 “allergic contact dermatitis”, L24 “irritant contact dermatitis”, L25 “unspecified contact dermatitis”, L26 “exfoliative dermatitis”, L27 “dermatitis due to substances taken internally”, L28 “lichen simplex chronicus and prurigo”, L29 “pruritus”, L30 “other dermatitis” (except L308C), L40 – L45 “papulosquamous disorders”, L53 “other erythematous conditions”, L55 “sunburn”, L56 “other acute skin changes due to ultraviolet radiation”, L80 “vitiligo”, L90 “atrophic disorders of the skin”, L93 “lupus erythematosus”

OR/AND

Exclusion medication criteria:

≥1 filled prescription of either:

D05 “antipsoriasisics” or D02AF “salicylates for dermatological use” or D07XB “corticosteroids moderate or potent other combinations” or D07XC “corticosteroids moderate or potent other combinations” or D07AD01 “corticosteroids (group IV) clobetasol” or D07CD01 “clobetasol and antibiotics”) AND D01 “antifungals” (implies corticosteroid (group IV) use for vaginal fungal infection)

*For prescription of corticosteroid group IV, a filled prescription of group I-III should also be used (as atopic dermatitis is never treated alone with group IV)

Algorithm to define children with asthma

Children with asthma fulfilled either criterion 1 and/or 2 below:

CRITERIA 1 (based on ICD-10):

≥1 hospital contact for:

J45.0 "allergic asthma"

J45.1 "non-allergic asthma"

J45.8 "asthma, different types"

J45.9 "asthma, unspecified"

J46.0 "status asthmaticus"

J46.9 "status asthmaticus, unspecified"

CRITERIA 2 (based on ATC):

> 1 filled prescription within 12 months of:

R03BA01 – R03BA08 "inhaled glucocorticoids"

R03DC01 – R03DC04 "leukotriene-receptor antagonists"

R03DC03 "montelukast (if no diagnosis of J30 allergic rhinitis)"

R03DB04 "theophylline og adrenergics"

R03DA54 "theophylline, combinations excl. psycholeptics"

R03BB01 "anticholinergica, Ipratropium bromide"

R03DX05 "omalizumab"

Algorithm to define children with allergic rhinoconjunctivitis

Children with allergic rhinoconjunctivitis fulfilled either criterion 1 – 4 below

CRITERIA 1 (based on ICD-10):

≥1 hospital contact for:

J30 “hay fever and allergic rhinitis”

J30.0 “vasomotor rhinitis”

J30.1 “allergic rhinitis due to pollen”

J30.2 “other seasonal allergic rhinitis”

J30.3 “other allergic rhinitis”

J30.4 “allergic rhinitis, unspecified”

J31.0 “chronic rhinitis”

CRITERIA 2 (based on ATC and ICD-10):

≥ 2 filled prescriptions of:

R01AD01 – R01AD60 “inhaled corticosteroids for rhinitis”

And no hospital contact for (exclusions criteria):

J33 “nasal polyps”

J330 “polyps in nasal cavity”

J331 “polyp related sinus degeneration”

J331A “Woakes' ethmoiditis”

J338 “nasal polyps, other”

J338A “polypus sinus sphenoidalis”

J339 “nasal polyps, unspecified”

J010- J019 “acute sinusitis”

J320 –J329 “chronic sinusitis”

CRITERIA 3 (based on ICD-10 and ATC)

≥2 filled prescriptions of:

R06A “antihistamines for systemic use”

And no hospital contact for:

L29 “pruritus” or

DL50 “allergic urticaria”

CRITERIA 4 (based on ATC)

≥ 1 filled prescriptions of:

V01A “specific immune therapy, allergen substrate therapy” or/and

S01GX “medication for allergic conjunctivitis”