

Population-based data on asthma and allergic disease call for advanced epidemiologic methods

Catarina Almqvist, MD, PhD,^{a,b} and Cecilia Lundholm, MSc^a *Stockholm, Sweden*

Key words: Register-based research, epidemiologic analysis, asthma incidence, medications, patient registers, allergic disease, children

Asthma and allergic diseases are common among children and adolescents worldwide.¹ Approximately 6% to 8% of Swedish and Danish children have asthma, and rhinitis and atopic dermatitis are even more common.^{1,2} Although the previous increase in asthma prevalence seems to have reached a plateau, variation in prevalence between genetically similar populations strongly implies that a substantial proportion is attributable to environmental aspects.³

It is of great importance to have valid measures of exposures, outcomes, and confounders and adequate sample sizes to study the causes and consequences of asthma and allergic disease. Many prospective birth cohorts, case-control studies, and randomized controlled trials have ascertained feasible associations from data collected through questionnaires and clinical examinations. In some countries these have been complemented by population-based information from medical records collected at antenatal clinics and hospital visits and information on prescribed drugs, all linked through personal identity numbers. Importantly, asthma outcomes have been well ascertained in validation studies through extensive linkages, medical record reviews, and algorithms.^{4,5} These register-based total population studies also allow comparison on asthma prevalence and incidence between different countries.

In a recent study by Henriksen et al,⁶ incidence rates of atopic dermatitis, asthma, and allergic rhinoconjunctivitis in the Danish and Swedish child populations are reported based on data from national registers. Incidence rates were ascertained through algorithms based on disease-specific dispensed prescribed medication, specific hospital contacts, or both. Findings were that the incidence rate of atopic dermatitis was stable and that allergic rhinoconjunctivitis decreased in both countries, whereas the incidence rate of asthma increased until 2006 and stabilized for the

rest of the study period in Denmark and increased in Sweden. The authors also report that at age 5 years, one third of all children were affected with at least 1 of the conditions.

The study shows that it is possible to assess patterns in the prevalence and incidence of asthma and allergic disease through population-based registers, but a few issues remain to acknowledge and discuss.

First, coverage of diagnoses in the Patient Registers (International Classification of Diseases, 10th revision) and medication in the Prescribed Drug Registers (Anatomical Therapeutic Chemical [ATC] classifications system) is of great importance. The authors have made a great effort to identify algorithms for the definition of atopic dermatitis, asthma, and allergic rhinoconjunctivitis. Although the algorithms are fairly inclusive, it seems feasible that they have conditioned at least 2 filled prescriptions of “corticosteroids for topical use” (ATC code D07) for atopic dermatitis and at least 2 prescriptions of “inhaled corticosteroids for rhinitis” (ATC code R01AD) or “antihistamines for systemic use” (ATC code R06A) for allergic rhinoconjunctivitis. When it comes to asthma controller medication, the frequency of distributions and selection of included medications become particularly important. The Swedish Patient Register covers all hospital visits and approximately 75% to 80% of outpatient visits to specialists but not those to primary health care. This is why dispensed medication from the Prescribed Drug Registers, which cover all health care facilities, is such an important source. In a recent validation study of asthma and atopic dermatitis, we concluded that asthma medication (≥ 2 filled prescriptions) is a suitable proxy for asthma, with a positive predictive value by predefined medication criteria that ranged between 0.75 and 0.94, depending on the age group. Meanwhile, medications for atopic dermatitis had a much lower positive predictive value.⁴ We based our validation on a large number of medical records that would be a great addition for this study, but in the meantime, we are very satisfied with the opportunity to have alternative measures of atopic dermatitis.

Another concern is that many of the drugs to treat atopic dermatitis and rhinoconjunctivitis have been provided over the counter (OTC), in Swedish pharmacies since 1992 and in supermarkets since 2009. Thus the incidence and prevalence of these diseases based on the Prescribed Drug Registers will be underestimated. Also, the authors have assessed rhinoconjunctivitis from birth, whereas it is more common that the disease starts later in preschool age. Hence although it is a clear advantage to have alternative measures of asthma and allergic disease, ideally, OTC sales should be considered when interpreting incidence trends. An increase in the proportion of OTC sales can otherwise be misinterpreted as a decrease in incidence rates.

Second, it is worth noting that the study populations were born during different time periods (1998-2011 in Denmark and 2006-2010 in Sweden). Thus the Danish data cover both preschooler

From ^athe Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, and ^bthe Lung and Allergy Unit, Astrid Lindgren Children's Hospital, Karolinska University Hospital.

Supported by the Swedish Research Council through the Swedish Initiative for Research on Microdata in the Social And Medical Sciences (SIMSAM; framework grant no. 340-2013-5867).

Disclosure of potential conflict of interest: C. Almqvist has received research support from the Swedish Research Council. C. Lundholm declares that she has no relevant conflicts of interest.

Received for publication June 1, 2015; accepted for publication June 4, 2015.

Corresponding author: Catarina Almqvist, MD, PhD, Department of Medical Epidemiology and Biostatistics, PO Box 281, Karolinska Institutet, SE 171 77 Stockholm, Sweden. E-mail: catarina.almqvist@ki.se.

J Allergy Clin Immunol 2015;■■■:■■■-■■■.

0091-6749/\$36.00

© 2015 American Academy of Allergy, Asthma & Immunology

<http://dx.doi.org/10.1016/j.jaci.2015.06.005>

and school-aged children from 2006 onward, whereas the Swedish data show incidence rate ratios (IRRs) for infants only (<1 year) in 2007 and the IRR for 2010 represents 0- to 3-year-olds. The Cox model ensures that each IRR is adjusted for age, but it cannot make up for such changes in age composition over time. Because the diseases have different phenotypes in preschooler and school-aged children and incidence differs with age, variations in age composition over time and between the countries might make overall comparisons difficult. It is worth noting that in the first few years of Danish data, when the same age groups are present as in the Swedish data, the incidence increase was similar, with a 30% increase for asthma from 1998-2002 (approximately $0.85/0.65 = 1.31$, see Fig 1 in the study by Henriksen et al⁶) compared with a 25% (IRR ≈ 1.25 , see Fig 1 in their study) increase in Sweden from 2006-2010. During the same periods, the incidence in atopic eczema was stable in both countries, whereas there was a markedly larger decrease in allergic rhinoconjunctivitis in Sweden (38%, IRR ≈ 0.62 , see Fig 1 in the study by Henriksen et al) than in Denmark (11%, approximately 1.05/1.18, see Fig 1 in their study). This can also be seen by comparing the shapes of the Swedish curves for 2006-2010 with those of the Danish curves for 1998-2002 in Fig 1 in the study by Henriksen et al.⁶ Comparing similar countries, as is done in this study, can improve our understanding of the diseases and the interpretation of the data. However, age-stratified IRR curves would be of great help for further understanding the incidence development in the 2 countries.

Finally, the authors claim there has been an increase in asthma incidence in Sweden over time, illustrated with a red line in their Fig 1.⁶ The increase seems to have been there only between 2009 and 2010, and because the incidence is not calculated for later years, it is difficult to claim an overall increase. Interestingly, the increase coincides with the swine flu pandemic, when Swedish residents were invited to immunize their young children.⁷ Also, public health information and surveillance was targeted toward infants and young children whose parents were advised to contact health care in case of respiratory symptoms related to influenza. We also know that the number of health care events and prescribed medication increased during this year, which might reflect the increase in asthma diagnoses and medication. In Denmark immunization was primarily targeted toward risk groups,⁸ and children in the Danish study population were older at the time of the influenza pandemic, possibly explaining why there is not a similar increase in asthma incidence during those years.

In conclusion, the study by Henriksen et al⁶ is of great interest and illustrates that despite some differences in population characteristics, incidence rates are fairly similar between the 2 countries. These results reinforce the possibilities to study the causes and consequences of these diseases in population-based register linkages. In doing so, sophisticated research methods, including family design, such as sibling comparison, can rule out alternative mechanisms that confound associations between early risks and later disease, including all unmeasured genetic and environmental factors shared by siblings, as we have recently shown for antibiotics⁹ and parental age.¹⁰ Some of the authors of this article also have expertise in twin design, which enables a particularly interesting sibling comparison. Most importantly, this article highlights the importance of using valid measures in register-based research and calls for advanced epidemiologic analyses methods now and in the future.

REFERENCES

1. Asher MI, Montefort S, Björkstén B, Lai CK, Strachan DP, Weiland SK, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet* 2006;368:733-43.
2. Bjerg A, Sandström T, Lundback B, Ronmark E. Time trends in asthma and wheeze in Swedish children 1996-2006: prevalence and risk factors by sex. *Allergy* 2010;65:48-55.
3. von Mutius E, Schmid S. The PASTURE project: EU support for the improvement of knowledge about risk factors and preventive factors for atopy in Europe. *Allergy* 2006;61:407-13.
4. Örtqvist 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.
5. Moth G, Vedsted P, Schiøtz P. Identification of asthmatic children using prescription data and diagnosis. *Eur J Clin Pharmacol* 2007;63:605-11.
6. Henriksen L, Simonsen J, Haerskjöld A, Linder M, Kieler H, Thomsen SF, et al. Incidence rates of atopic dermatitis, asthma, and allergic rhinoconjunctivitis in Danish and Swedish children. *J Allergy Clin Immunol* 2015;136:XXX-XXX.
7. Örtqvist AK, Berggren I, Insulander M, de Jong B, Svenungsson B. Effectiveness of an adjuvanted monovalent vaccine against the 2009 pandemic strain of influenza A(H1N1)v, in Stockholm County, Sweden. *Clin Infect Dis* 2011;52:1203-11.
8. Mereckienė J, Cotter S, Weber JT, Nicoll A, D'Ancona F, Lopalco PL, et al. Influenza A(H1N1)pdm09 vaccination policies and coverage in Europe. *Euro Surveill* 2012 Jan 26;17(4).
9. Örtqvist AK, Lundholm C, Kieler H, Ludvigsson JF, Fall T, Ye W, et al. Antibiotics in fetal and early life and subsequent childhood asthma: nationwide population based study with sibling analysis. *BMJ* 2014;349:g6979.
10. Almqvist C, Olsson H, Ullemar V, D'Onofrio B, Frans E, Lundholm C. The association between parental age and asthma in a population-based register study. *J Allergy Clin Immunol* 2015 [Epub ahead of print]. doi: <http://dx.doi.org/10.1016/j.jaci.2015.04.006>.

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”