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Population-based data on asthma and allergic disease calls for advanced epidemiological methods

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Asthma and allergic diseases are common among children and adolescents worldwide.[1] Approximately 6-8% of Swedish and Danish children have asthma, and rhinitis or 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]

In order to study causes and consequences of asthma and allergic disease, it is of great importance to have valid measures of exposures, outcomes and confounders and adequate sample sizes. Many prospective birth cohorts, case-control studies and randomized control trials have ascertained feasible associations from data collected through questionnaires and clinical examinations. In some countries, these have been complemented with population-based information from medical records collected at antenatal clinics and hospital visits, and to 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, incidence rates of atopic dermatitis, asthma and allergic rhinoconjunctivitis in the Danish and Swedish child populations are reported based on data from national registers.[6] Incidence rates were ascertained through algorithms based on disease-specific dispensed prescribed medication and/or specific hospital contacts. Findings were that incidence rate of atopic dermatitis was stable and 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. They also report that at age 5 years, one third of all children were affected with at least one of the conditions.

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

Firstly, coverage of diagnoses in the Patient Registers (International Classification of Diseases, 10th revision, ICD-10) 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 definition of atopic dermatitis, asthma and allergic rhinoconjunctivitis. Although the algorithms are fairly including it seems feasible that they have conditioned at least two filled prescriptions of "corticosteroids for topical use" (ATC-code D07) for atopic dermatitis and at least two prescriptions for "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 becomes particularly important. The Swedish Patient register covers all hospital visits and approximately 75-80% of outpatient visits to specialists but not those to primary health care. This is why dispensed medication from the Prescribed Drug Registers, which covers all health care facilities, is such an important source. In a recent validation study of asthma and atopic dermatitis, we concluded that asthma medication (≥ two filled prescriptions) is a suitable proxy for asthma with a positive predicted value (PPV) by predefined medication criteria that ranged between 0.75 and 0.94 depending on age group. Meanwhile, medications for atopic dermatitis had a much lower PPV.[4] We based our validation on a large number of medical records which would be a great addition also 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 can be provided over the counter (OTC) in Swedish pharmacies since 1992 and in supermarkets since 2009. Thus, 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, while 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.

Secondly, it is worth noting that the study populations were born during different time periods; in Denmark 1998-2011 and in Sweden 2006-2010. Thus, the Danish data covers both preschoolers and school-age children from 2006 and onwards, while the Swedish shows the incidence rate ratios (IRR) for infants only (< 1 year) in 2007 and the IRR for 2010 represents 0-3 year olds. The Cox model ensures that each IRR is adjusted for age, but it cannot make up for such changes in the age composition over time. Since the diseases have different phenotypes in preschoolers and school age children and incidence differs with age, variations in age composition over time and between the countries may make overall comparisons difficult. It is worth noting that in the first few years of Danish data, where the same age groups are present as in the Swedish data, the incidence increase is similar, with 30% increase for asthma from 1998-2002 (Figure 1: ~0.85/0.65=1.31), as compared to 25% (Figure 1: IRR≈1.25) increase 2006-2010 in Sweden. During the same periods the incidence in atopic eczema is stable in both countries, while there is a markedly larger decrease in allergic rhinoconjunctivitis in Sweden (38%, Figure 1: IRR≈0.62) than in Denmark (11%, Figure 1: ~1.05/1.18). 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 Figure 1. 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 incidence rate ratio curves would be of great help for further understanding of the incidence development in the two countries.

Finally, the authors claim there has been an increase in asthma incidence in Sweden over time, illustrated with a red line in their Figure 1. The increase seems to have been there only between 2009 and 2010, and since 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 little children.[7] Also, public health information and surveillance was targeted towards 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 may reflect the increase in asthma diagnoses and medication. In Denmark, immunization was primarily targeted towards 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 rise in asthma incidence during those years.

In conclusion, the study is of great interest and illustrates that despite some differences in population characteristics the incidence rates are fairly similar between the two countries. The results reinforce the possibilities to study 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 such as we have recently shown for antibiotics[9] and parental age.[10] Some of the authors of this paper 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

epidemiological analyses methods now and in the future.

References

1. Asher MI, Montefort S, Bjorksten B, 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**(9537): 733-43.
2. Bjerg A, Sandstrom 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**(1): 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**(4): 407-13.
4. 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**(8): 850-60.
5. Moth G, Vedsted P, Schiotz P. Identification of asthmatic children using prescription data and diagnosis. *Eur J Clin Pharmacol* 2007; **63**(6): 605-11.
6. Henriksen L, Simonsen J, Haerskjold A, et al. Incidence rates of atopic dermatitis, asthma, and allergic rhinoconjunctivitis in Danish and Swedish children. *J Allergy Clin Immunol* 2015.
7. Ortqvist A, 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. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2011; **52**(10): 1203-11.
8. Mereckiene J, Cotter S, Weber JT, et al. Influenza A(H1N1)pdm09 vaccination policies and coverage in Europe. *Euro surveillance : bulletin Europeen sur les maladies transmissibles = European communicable disease bulletin* 2012; **17**(4).
9. Ortqvist AK, Lundholm C, Kieler H, 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; **In Press**.