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Upper airway and skin symptoms in allergic and non-allergic asthma: results from the Swedish GA²LEN study

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ABSTRACT

Background: Allergic and non-allergic asthma are viewed as separate entities, despite sharing similarities. The aims of this study were to determine differences in symptoms from the upper airways and the skin in allergic and non-allergic asthma. The secondary aims were to identify childhood risk factors and to compare quality of life in the two asthma groups.

Methods: This cohort (age 17-76 years) consisted of 575 subjects with allergic or non-allergic asthma and 219 controls. The participants participated in an interview, spirometry, exhaled nitric oxide (NO), skin prick test and responded to the Mini Asthma Quality of Life Questionnaire.

Results: Self-reported allergic rhinitis was significantly more common in both allergic and non-allergic asthma (82.3% and 40.7%) compared with the controls. The prevalence of chronic rhinosinusitis (CRS) was similar in both asthma groups. Eczema was significantly more common in both asthmatic groups (72.3% and 59.8%) than controls (47.0%) ($p < 0.001$ and $p = 0.012$). Severe respiratory infection in childhood and parental allergy were risk factors for both allergic and non-allergic asthma. Quality of life was significantly lower in non-allergic than allergic asthma ($p = 0.01$).

Conclusion: Concomitant symptoms from the upper airways and the skin were significantly more common in both allergic and non-allergic asthma. This indicates that non-allergic asthma has a systemic component with similarities to what is found in allergic asthma. There were similarities in the childhood risk factor pattern between the two types of asthma but asthma-related quality of life was lower in the non-allergic asthma group.

INTRODUCTION

Asthma is a worldwide disease affecting more than 300 million people, as well as being a global public health issue with a major socio-economic impact on both patients and society (1). The disease is regarded as a chronic inflammatory disorder of the airways leading to bronchial hyperresponsiveness, remodelling and a reduction in lung function when not properly managed (2). Allergic and non-allergic asthma are often viewed as distinct diseases, i.e. expressing different phenotype characteristics, based on a skin prick test and IgE levels (3). Several studies also show pathophysiological differences (4-7). Studies have also reported differences in risk factors, especially those related to the childhood environment (8,9), between these two asthma phenotypes. In these two studies in Swedish children the association between infections, pets and parental smoking was stronger to non-allergic than allergic asthma (8,9).

Allergic asthma and its association with the upper airways have been explored extensively over the last two decades and the presence of concomitant allergic rhinitis is common (10), suggesting that asthma with rhinitis is an allergic united airways disease (11- 13). Non-allergic asthma, on the other hand, has been investigated to a far lesser degree in this respect (14), although some studies have shown a high prevalence of rhinitis and rhinosinusitis among patients with non-allergic asthma (15-17). It is also well known that eczema is associated with other atopic diseases, such as allergic asthma and allergic rhinitis (18), but less is known about its association with non-allergic asthma (19).

The primary aim of the study was to determine differences in symptoms from the upper airways and the skin in allergic and non-allergic asthma. The secondary aim was to identify childhood

risk factor profiles for allergic vs non-allergic asthma and the third aim was to compare quality of life in the two asthma groups.

MATERIAL AND METHODS

Study design

The Global Allergy and Asthma European Network (GA²LEN) cross-sectional survey was carried out in 2008 by mailing a postal questionnaire to a random sample of adults aged 15-75 years (14). A clinical follow-up study was conducted in 2008-2010 in a randomly selected subgroup with reported symptoms of asthma, rhinitis, chronic rhinosinusitis (CRS) and eczema in 19 European centres. In Sweden, four centres participated (Gothenburg, Stockholm, Umeå and Uppsala) and 27,866 persons responded (60% response rate) to the initial postal survey in 2008, of whom 1,329 participated in a clinical follow-up study (20).

Clinical study

Subjects that participated in the clinical follow-up took part in a structured interview and a clinical investigation with a skin prick test, blood sampling and spirometry. In Sweden, the follow-up also included measurements of exhaled nitric oxide and assessments of asthma-specific quality of life (20).

Questionnaire

The GA²LEN follow-up questionnaire included validated questions related to respiratory symptoms, rhinitis, CRS and eczema, as well as demographic data. The questions were based on those in the European Community Respiratory Health Survey (ECRHS) (15, 21) and included

questions on respiratory symptoms, family history of asthma, diagnosed asthma, the use of asthma medications, history of allergy and sinusitis, history of eczema, smoking history and occupation.

Asthma was defined as a self-reported diagnosis *and* asthma symptoms *or* asthma treatment in the last 12 months. Asthma symptoms were defined as wheeze, attacks of shortness of breath or night awakening with shortness of breath/cough.

Allergic rhinitis was defined as a positive response to the question: Do you have any nasal allergies or hay fever?

Non-infectious rhinitis was defined as a positive response to ever having problems with sneezing, or a runny or a blocked nose when not having a cold or flu *or* ever having problems with sneezing, or a runny or a blocked nose when not having a cold or flu during the last 12 months.

Rhinoconjunctivitis was defined as ever having problems with sneezing, or a runny or a blocked nose when not having a cold or flu during the last 12 months *and* accompanied by itchy or watery eyes.

Chronic rhinosinusitis (CRS) was defined according to the European Position Paper on Rhinosinusitis and Nasal Polyps (EP3OS criteria) (22), with the presence of at least two of the following symptoms for at least 12 weeks in the past 12 months: nasal blockage, nasal discharge, facial pain or pressure and reduction of sense of smell with *at least one* of the symptoms being nasal blockage or nasal discharge.

Eczema was defined as a positive response to ever having eczema or any kind of skin allergy or ever having an itchy rash that came and went for at least six months (23).

Itchy rashes were defined as ever having an itchy rash that came and went for the last six months or having had this itchy rash in the last 12 months (23).

Childhood factors

The following childhood-related variables were assessed.

Parental asthma. “Did your mother or father *ever* have asthma?”

Parental allergy. “Did your mother or father *ever* have eczema, skin or nasal allergy or hay fever?”

Day care. “Did you go to a school, play-school or nursery with *older* children before the age of five years?”

Shared bedroom. “Did you regularly share your bedroom with any *older* children before the age of five years?”

House pets. “Was there a dog or cat in your home during your first year of life?”

Raised on a farm. “Which term best describes the place you lived most of the time when you were under the age of five years?”

Severe respiratory infection in childhood. “Did you have a serious respiratory infection before the age of five years?”

Hospitalisation in childhood. “Were you hospitalised before the age of two years for lung disease?”

Skin prick test

A skin prick test (SPT) was performed on the inside of the forearm using a standard set of aeroallergens for the GA²LEN network (24): timothy, mixed grass, *Dermatophagoides pteronyssinus*, cat, birch, blatella, olive, *Alternaria*, dog, *Artemesia*, parietaria, *Dermatophagoides farinae*, histamine (positive control) and diluent (negative control). Standardized extracts from ALK Abelló (Hamburg, Germany), Allergopharma (Reinbek, Germany), Leti Pharma (Witten, Germany) and Stallergènes (Antony, France) were used. The largest and perpendicular diameters of the wheal elicited by the allergens were measured and the mean value was calculated. A positive wheal was defined as ≥ 3 mm, if the control solutions showed the expected result, i.e. histamine ≥ 3 mm and negative control < 3 mm. Atopy was defined as the presence of at least one positive SPT wheal.

Fraction of exhaled NO (FeNO) and total IgE

FeNO was assessed using NIOX MINO, Aerocrine, Stockholm, Sweden, according to the American Thoracic Society (ATS) and European Respiratory Society (ERS) recommendations (25). Blood sampling for measurements of total IgE was performed using ImmunoCAP® (former RAST), (Phadia Diagnostics AB/ThermoFisher, Uppsala, Sweden).

Spirometry

Lung function measurements were performed using the EasyOne™ Spirometer (Ndd Laboratories, Medizintechnik AG, Zurich, Switzerland) with a daily calibration check. Forced vital capacity (FVC) and forced expiratory volume in one second (FEV₁) were measured, at least three times each before and at least after 15 minutes after bronchodilatation with 200 µg of salbutamol. The FEV₁, FVC, FEV₁/FVC were measured according to the ATS/ERS guidelines (26). Height and weight were measured and body mass index (BMI) was calculated.

Mini-AQLQ

All subjects fulfilling the criteria for asthma in the postal survey also completed the Mini Asthma Quality of Life Questionnaire (mini-AQLQ) (27). Subjects were asked to assess functional impairment due to their asthma during the last two weeks by responding to 15 questions grouped into four domains on a seven-point scale. The four domains are: symptoms (5 items), activity limitations (4 items), emotional function (3 items) and environmental stimuli (3 items). Each question was scored from severe impairment (1) to no impairment (7) and the mean overall score was calculated.

Bronchial responsiveness

Bronchia responsiveness was assessed by methacholine test in a subsample of asthmatics (n = 55) from one of the centres (Stockholm). Inhalation challenges were performed by using a dosimeter-controlled jet nebulizer (Spira Electro 2; Respiratory Care Center, Hameenlinna, Finland) and with pulmonary function measured as FEV₁. Challenges started by inhalation of the diluent. Provided the FEV₁ did not change by more than 10%, inhalation of methacholine or the

allergen to which the subjects were sensitized was commenced with the postdiluent FEV1 value used as baseline. Half-log increments in the cumulated dose of allergen were inhaled every 15 minutes (7-7100 SQ units), whereas methacholine was administered every third minute in doubling doses (14.2-7256 mg). The challenge was stopped when the FEV1 had fallen by at least 20%. The PD20 value was derived by linear interpolation from the log cumulated dose-response curve.

Sample selection

In the present study, three groups of participants were studied.

Allergic asthma: participants that fulfilled the definition of asthma and had a positive SPT (n = 401).

Non-allergic asthma: participants that fulfilled the definition of asthma and had a negative SPT (n = 174).

Control group: participants that were not classified as having asthma or CRS and who did not report attacks of shortness of breath, wheezing, use of asthma medicines, or CRS symptoms constituted the control group (n = 219) (20).

Statistical analyses

All analyses were performed using STATA 12 (STAT Corp, College Station, Texas, USA). FeNO was log transformed. The differences between groups were tested using either a chi-square test or analysis of variance (ANOVA). Multiple nominal and bi-nominal logistic regressions were used in the multivariate analyses. A p-value of < 0.05 was considered significant.

Ethics

The study was approved by the Regional Ethical Review Board in Stockholm, Sweden (Dnr 2008/1100-31/4).

RESULTS**General characteristics**

Among subjects with asthma, 70% (n = 401) had allergic asthma and 30% (n = 174) non-allergic asthma, according to the predefined criteria. The allergic asthma group was significantly younger compared with the non-allergic asthma group and the control group (Table 1). BMI was significantly higher in both allergic and non-allergic asthma compared with the control group and significantly higher in non-allergic asthma compared with allergic asthma (Table 1). Current smoking was significantly more common in non-allergic asthma compared with allergic asthma, but no significant difference was found between the controls and any of the two asthma groups (Table 1). FEV₁ was significantly lower in allergic and non-allergic asthma compared with the controls and lower in the non-allergic group compared with the allergic asthma group. FeNO was significantly higher in allergic asthma compared with non-allergic asthma (Table 1). The difference in age, current smoking and FeNO remained statistically significant between allergic and non-allergic asthma after adjusting for age, gender, BMI and smoking history, whereas no significant difference regarding BMI and lung function was found between the two asthma groups after these adjustments. Bronchial responsiveness was higher in the allergic than the non-allergic asthma group. This difference was of border line significance in the univariate analysis

but became significant after adjusting for age, gender, BMI and smoking history (Beta coefficient (95% CI) 0.80 (0.20-1.40), $p = 0.01$)

Rhinitis and skin symptoms

Allergic rhinitis and non-infectious rhinitis were significantly more common in both allergic and non-allergic asthma compared with the control group and more prevalent in the group with allergic asthma compared with the group with non-allergic asthma. The prevalence of CRS was similar in both asthmatic groups (Table 2). Eczema, ever having itchy rashes for more than six months and having itchy rashes for more than 12 weeks during the last 12 months were more common in both asthmatic groups than among the controls. These differences remained significant after adjusting for age, gender, BMI and smoking history (Figure 1).

Rhinitis and skin symptoms are combined in the Venn diagrams in Figure 2. Only 14% of the participants with allergic asthma did not have allergic rhinitis or an itchy rash in the last 12 months, while the corresponding figure for non-allergic asthma was 45%. The level of total IgE and FeNO was studied in these groups. Total IgE increased with the level of rhinitis and skin engagement increased in the allergic asthma group, while a trend towards higher FeNO in the participants with both rhinitis and a rash was found in the non-allergic asthma group (Table 3).

Childhood risk factors

The mean age of asthma onset was lower in the allergic group than the non-allergic asthma group (17.8 ± 0.7 vs. 30.4 ± 1.4 years, $p < 0.001$). Parental asthma was an independent risk factor for both allergic and non-allergic asthma, but it was significantly more common in allergic asthma

than non-allergic asthma (Table 4). Maternal and paternal asthma and allergy had a relative similar association to allergic and non-allergic asthma with one exception. Father's allergy was significantly associated to allergic asthma but not to non-allergic asthma (adjusted odds ratio (95% confidence interval): 3.78 (2.29-6.23) and 0.98 (0.55-1.75), respectively). Being raised on a farm and attending day care before the age of five years were both independent risk factors for non-allergic asthma but not for allergic asthma. Having had a severe respiratory infection before the age of five years and hospitalisation due to lung disease before the age of two years were both independent risk factors for both allergic and non-allergic asthma, without differences between the two asthma groups (Table 4). No significant association between parental smoking and asthma was detected.

Quality of life

The overall mini-AQLQ scores were significantly lower in non-allergic asthma compared with allergic asthma, as well as in all four domains (symptoms, activity limitations, emotional function and environmental stimuli), and this also remained significant after adjusting for age, gender, BMI and smoking history, except for the emotional domain (Table 5).

DISCUSSION

The main finding in this investigation was that concomitant symptoms from the upper airways and skin were significantly more common in both allergic and non-allergic asthma. In addition, there were similarities in early childhood events, as well as in parental history of asthma and allergy in allergic and non-allergic asthma. Subjects with non-allergic asthma were older, were

more likely to have been raised on a farm and had poorer asthma-related quality of life than those with allergic asthma.

Upper airway symptoms such as rhinitis and rhinoconjunctivitis were significantly more common in both the allergic and non-allergic asthma groups compared with controls, although they were more common in allergic asthma than in the non-allergic group. CRS was also common in both asthma groups but without any difference in prevalence between allergic and non-allergic asthma. Epidemiological CRS data are sparse, but, in 2012, Jarvis *et al.* showed a strong association between CRS and asthma (16) and, furthermore, non-allergic CRS has been associated with late-onset non-allergic asthma (28). The current thinking regards rhinitis, CRS and asthma as overlapping syndromes, with distinct clinical phenotypes and biological endotypes (28). This united airways concept has been extensively explored during the last decade. However, less is known about the association between non-allergic asthma and rhinitis and CRS and it has been speculated that airway diseases are united beyond atopic connections (14, 29). For example, CRS can develop independently of allergy (30), but, interestingly, IgE-mediated pathways are thought to play a role in the pathogenesis even in non-allergic CRS (22).

Skin disorders such as eczema and itchy rashes were significantly more common in both asthmatic groups. Eczema and its link to atopy is currently considered relatively weak and only approximately one third of patients have measurable levels of allergen-specific IgE (18). This is in line with studies questioning “the atopic march” from eczema in childhood to rhinitis and asthma (31). One key novel finding in our current study is the apparent connection between non-atopic asthma and eczema and rashes. The existence of systemic allergic inflammation in allergic

asthma and allergic rhinitis is well accepted, but it has not been assessed in large population samples in non-allergic asthma. However, recent studies have reported the presence of systemic inflammation in patients with CRS, with or without polyps, and they have speculated about global airway disease beyond allergy (32). A defective epithelial skin function due to filaggrin loss-of-function mutations has recently been recognised as a cause of atopic dermatitis (33) and studies have demonstrated elevated levels of IgE in subjects with filaggrin null mutations (34), which are also associated with allergic asthma (33). As a result, defective epithelial barriers in the airways and skin could account for the co-existence of asthma and skin disorders in both allergic and non-allergic asthma.

In this study, having a severe respiratory infection before the age of five years, as well as hospitalisation because of lung disease before two years of age, were independent risk factors for both allergic and non-allergic asthma, with no difference between the two asthma groups. It has been postulated that infectious key events in early childhood can have an impact on subsequent allergic sensitisation and asthma development (35). In a Swedish study following a cohort of infants admitted to hospital for respiratory syncytial virus (RSV) bronchiolitis, the children had increased frequencies of recurrent wheeze, asthma and allergic sensitisation throughout childhood (36). The same thing was demonstrated in a birth cohort of children with an increased risk of asthma, with regard to lower respiratory tract infections with rhinovirus (37).

Both parental allergy and parental asthma were independent risk factors for allergic and non-allergic asthma. These results are consistent with previous studies reporting parental asthma (38) and parental atopy (39) as independent risk factors for asthma in offspring. Having been raised

on a farm and attending day care before five years of age were independent risk factors for non-allergic asthma but not for allergic asthma in our study population. The protective effect of *early* childhood farm exposure, especially during the first year of life, on allergic sensitisation has been supported by many previous studies (40,41). Epidemiological cross-sectional studies in adulthood may also be influenced by environmental and occupational exposure later in life, modifying early life exposure with regard to both allergic and non-allergic asthma.

The non-allergic asthma group had poorer asthma-related quality of life compared with the group with allergic asthma. These findings also remained after adjusting for age, BMI and smoking history and are consistent with previous studies finding that non-allergic asthma is often more severe than allergic asthma (42). Risk factors differing between allergic and non-allergic asthma, i.e. a history of tobacco smoke and central obesity, could partly explain these findings and may contribute to a more difficult-to-treat and control asthma phenotype, resulting in poorer quality of life (43). Another explanation could be undiagnosed and untreated concomitant sino-nasal disease (20), often disregarded in non-allergic asthma, as the united airways concept in non-allergic asthma is less studied (14).

In this Swedish cohort, 70% had allergic asthma and 30% non-allergic asthma, which are in the same relative range previously reported for adults (44). Subjects with allergic asthma were significantly younger and reported having their first asthma attack at a younger age than those with non-allergic asthma. BMI was higher in both asthma groups, which is in accordance with some previous reports (9,45), but different from a recent report in children where obesity was related to allergic but not to non-allergic asthma (46). Moreover, current smoking was

significantly higher in non-allergic asthma than allergic asthma and this is also consistent with previously reported findings (44,45). FeNO was significantly higher in allergic asthma compared with non-allergic asthma and this result is in accordance with previous studies (9,49), as FeNO is regarded as a marker of Th2-driven eosinophil airway inflammation (48). Nevertheless, increased levels of FeNO have also been reported in non-smoking, non-allergic asthma (49). In the present study, there was a trend towards higher FeNO levels in non-atopic asthmatics with rhinitis and skin symptoms.

One of the strengths of this Swedish multi-centre cohort lies in the quality of the standardised GA²LEN survey data collected, the population-based design and the age range from 17 to 76 years, i.e. also including older asthma patients who are of special concern and much less studied. In addition to questions validated by the GA²LEN network, subjects had a clinical follow-up and the investigated Swedish cohort can be regarded as relatively homogeneous, as data from the centres are consistent. Another strength of this cross-sectional study is the simultaneous evaluation of asthma with upper airways and skin allergy, as well as risk factors for allergic and non-allergic asthma in a large population sample. Naturally, these data must be interpreted with care, especially when studying associations between complex and multifactorial diseases, as associations at individual level can differ due to confounding factors and exposure is not fully assessed. The division of asthma groups into allergic and non-allergic is traditionally based on the concomitant presence of atopy, i.e. skin test positivity for at least one aeroallergen in epidemiological studies. It is, however, known that the presence of atopy alone cannot be used to divide asthmatics into the allergic and non-allergic phenotypes (50), as atopy can be a co-

morbidity and without any causal link to asthma. The definition of CRS is based on questionnaire, but this definition has been validated against objective measurements (51).

To summarise, the main finding in this clinical follow-up of the Swedish multicentre GA²LEN survey is that concomitant symptoms from the upper airways and skin are significantly more common in both allergic and non-allergic asthma than in non-asthmatics. This indicates that non-allergic asthma also has a systemic component with similarities to allergic asthma. Further studies are needed to detect the underlying mechanism of this systemic component. Despite the fact that allergic asthma had a much earlier onset than non-allergic asthma, there were similarities in the childhood risk factor pattern. One important difference between the two types of asthma, however, is the poorer asthma-related quality of life in the non-allergic asthma group.

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Declaration of interest

Kjell Alving has received consultancy fees from Aerocrine AB (producer of exhaled NO devices). None of the funding agencies or industry partners had any role in study design, data

collection and analysis, decision to publish or preparation of the manuscript. None of the other authors have any conflict of interest to declare with regard to present manuscript.

REFERENCES

1. Accordini S, Corsico AG, Braggion M, Gerbase MW, Gislason D, Gulsvik A, Heinrich J, Janson C, Jarvis D, Jøgi R, Pin I, Schoefer Y, Bugiani M, Cazzoletti L, Cerveri I, Marcon A, de Marco R. The cost of persistent asthma in Europe: an international population-based study in adults. *Int Arch Allergy Immunol*. 2013;160:93-101.
2. Global Initiative for Asthma. 2017 GINA Report, Global Strategy for Asthma Management and Prevention. 2017; Available from: <http://ginasthma.org/2017-gina-report-global-strategy-for-asthma-management-and-prevention/> [last accessed 12 April 2017].
3. Romanet-Manent S, Charpin D, Magnan A, Lanteaume A, Vervloet D; EGEA Cooperative Group. Allergic vs nonallergic asthma: what makes the difference? *Allergy*. 2002;57:607-613.
4. Amin K, Lúdvíksdóttir D, Janson C, Nettelbladt O, Björnsson E, Roomans GM, Boman G, Sevéus L, Venge P. Inflammation and structural changes in the airways of patients with atopic and nonatopic asthma. BHR Group. *Am J Respir Crit Care Med*. 2000;162:2295-2301.
5. Lúdvíksdóttir D, Janson C, Högman M, Hedenström H, Björnsson E, Boman G. Exhaled nitric oxide and its relationship to airway responsiveness and atopy in asthma. BHR-Study Group. *Respir Med*. 1999;93:552-556.
6. Olafsdottir IS, Gislason T, Thjodleifsson B, Olafsson I, Gislason D, Jøgi R, Janson C. C reactive protein levels are increased in non-allergic but not allergic asthma: a multicentre epidemiological study. *Thorax*. 2005;60:451-454.

7. Janson C. Phenotypes of obstructive lung disease. *Clin Respir J*. 2008;2 Suppl 1:88-91
8. Rönmark E, Jönsson E, Platts-Mills T, Lundbäck B. Different pattern of risk factors for atopic and nonatopic asthma among children--report from the Obstructive Lung Disease in Northern Sweden Study. *Allergy*. 1999;54:926-935
9. Janson C, Kalm-Stephens P, Foucard T, Alving K, Nordvall SL. Risk factors associated with allergic and non-allergic asthma in adolescents. *Clin Respir J*. 2007;1:16-22.
10. Porsbjerg C, Menzies-Gow A. Co-morbidities in severe asthma: Clinical impact and management. *Respirology* 2017 (in press)
11. Braunstahl GJ, Fokkens WJ, Overbeek SE, KleinJan A, Hoogsteden HC, Prins JB. Mucosal and systemic inflammatory changes in allergic rhinitis and asthma: a comparison between upper and lower airways. *Clin Exp Allergy*. 2003;33:579-587.
12. Bousquet J, Vignola AM, Demoly P. Links between rhinitis and asthma. *Allergy*. 2003;58:691-706
13. Brozek JL, Bousquet J, Baena-Cagnani CE, Bonini S, Canonica GW, Casale TB, van Wijk RG, Ohta K, Zuberbier T, Schünemann HJ; Global Allergy and Asthma European Network; Grading of Recommendations Assessment, Development and Evaluation Working Group. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision. *J Allergy Clin Immunol*. 2010;126:466-476.

14. Hens G, Vanaudenaerde BM, Bullens DM, Piessens M, Decramer M, Dupont LJ, Ceuppens JL, Hellings PW. Sinonasal pathology in nonallergic asthma and COPD: 'united airway disease' beyond the scope of allergy. *Allergy*. 2008;63:261-267.

15. Bjerg A, Ekerljung L, Middelveld R, Dahlén SE, Forsberg B, Franklin K, Larsson K, Lötval J, Olafsdóttir IS, Torén K, Lundbäck B, Janson C. Increased prevalence of symptoms of rhinitis but not of asthma between 1990 and 2008 in Swedish adults: comparisons of the ECRHS and GA²LEN surveys. *PLoS One*. 2011;6:e16082.

16. Jarvis D, Newson R, Lotvall J, Hastan D, Tomassen P, Keil T, Gjomarkaj M, Forsberg B, Gunnbjornsdottir M, Minov J, Brozek G, Dahlen SE, Toskala E, Kowalski ML, Olze H, Howarth P, Krämer U, Baelum J, Loureiro C, Kasper L, Bousquet PJ, Bousquet J, Bachert C, Fokkens W, Burney P. Asthma in adults and its association with chronic rhinosinusitis: the GA2LEN survey in Europe. *Allergy*. 2012;67:91-98.

17. Obaseki D, Potts J, Joos G, Baelum J, Haahtela T, Ahlström M, Matricardi P, Kramer U, Gjomarkaj M, Fokkens W, Makowska J, Todo-Bom A, Toren K, Janson C, Dahlen SE, Forsberg B, Jarvis D, Howarth P, Brozek G, Minov J, Bachert C, Burney P; GA2LEN network of excellence. The relation of airway obstruction to asthma, chronic rhinosinusitis and age: results from a population survey of adults. *Allergy*. 2014;69:1205-1214.

18. Johansson SG, Flohr C, Wahlgren CF, Williams H. Role of immunoglobulin E sensitization in eczema, previously referred to as atopic dermatitis. *Expert Rev Clin Immunol*. 2005;1:257-262.

19. Sinisgalli S, Collins MS, Schramm CM. Clinical Features Cannot Distinguish Allergic from Non-allergic Asthma in Children. *J Asthma* 2012;49:51-56.
20. Ek A, Middelveld RJ, Bertilsson H, Bjerg A, Ekerljung L, Malinovschi A, Stjärne P, Larsson K. Chronic rhinosinusitis in asthma is a negative predictor of quality of life: results from the Swedish GA(2)LEN survey. *Allergy*. 2013;68:1314-1321.
21. Burney PG, Laitinen LA, Perdrizet S, Huckauf H, Tattersfield AE, Chinn S, Poisson N, Heeren A, Britton JR, Jones T. Validity and repeatability of the IUATLD (1984) Bronchial Symptoms Questionnaire: an international comparison. *Eur Respir J*. 1989;2:940-945.
22. Fokkens WJ, Lund VJ, Mullol J, Bachert C, Alobid I, Baroody F, Cohen N, Cervin A, Douglas R, Gevaert P, Georgalas C, Goossens H, Harvey R, Hellings P, Hopkins C, Jones N, Joos G, Kalogjera L, Kern B, Kowalski M, Price D, Riechelmann H, Schlosser R, Senior B, Thomas M, Toskala E, Voegels R, Wang de Y, Wormald PJ. European Position Paper on Rhinosinusitis and Nasal Polyps 2012. *Rhinol Suppl*. 2012;(23):1-298.
23. Harrop J, Chinn S, Verlato G, Olivieri M, Norbäck D, Wjst M, Janson C, Zock JP, Leynaert B, Gislason D, Ponzio M, Villani S, Carosso A, Svanes C, Heinrich J, Jarvis D. Eczema, atopy and allergen exposure in adults: a population-based study. *Clin Exp Allergy*. 2007;37:526-535.
24. Heinzerling LM, Burbach GJ, Edenharter G, Bachert C, Bindslev-Jensen C, Bonini S, Bousquet J, Bousquet-Rouanet L, Bousquet PJ, Bresciani M, Bruno A, Burney P, Canonica GW, Darsow U, Demoly P, Durham S, Fokkens WJ, Giavi S, Gjomarkaj M, Gramiccioni C, Haahtela T, Kowalski ML, Magyar P, Muraközi G, Orosz M, Papadopoulos NG, Röhnelt C, Stingl G,

Todo-Bom A, von Mutius E, Wiesner A, Wöhrl S, Zuberbier T. GA(2)LEN skin test study I: GA(2)LEN harmonization of skin prick testing: novel sensitization patterns for inhalant allergens in Europe. *Allergy*. 2009;64:1498-1506.

25. ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005. American Thoracic Society; European Respiratory Society. *Am J Respir Crit Care Med*. 2005;171:912-930.

26. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CP, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger J; ATS/ERS Task Force. Standardisation of spirometry. *Eur Respir J*. 2005;26:319-338.

27. Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. *Eur Respir J*. 1999;14:902-907.

28. Kariyawasam HH, Rotiroti G. Allergic rhinitis, chronic rhinosinusitis and asthma: unravelling a complex relationship. *Curr Opin Otolaryngol Head Neck Surg*. 2013 ;21:79-86.

29. Braunstahl GJ. Chronic rhinosinusitis, nasal polyposis and asthma: the united airways concept reconsidered? *Clin Exp Allergy*. 2011;41:1341-1343.

30. Feng CH, Miller MD, Simon RA. The united allergic airway: connections between allergic rhinitis, asthma, and chronic sinusitis. *Am J Rhinol Allergy*. 2012;26:187-190.

31. Hopper JL, Bui QM, Erbas B, Matheson MC, Gurrin LC, Burgess JA, Lowe AJ, Jenkins MA, Abramson MJ, Walters EH, Giles GG, Dharmage SC. Does eczema in infancy cause hay fever, asthma, or both in childhood? Insights from a novel regression model of sibling data. *J Allergy Clin Immunol*. 2012;130:1117-1122.
32. Hellings PW, Fokkens WJ, Akdis C, Bachert C, Cingi C, Dietz de Loos D, Gevaert P, Hox V, Kalogjera L, Lund V, Mullol J, Papadopoulos NG, Passalacqua G, Rondón C, Scadding G, Timmermans M, Toskala E, Zhang N, Bousquet J. Uncontrolled allergic rhinitis and chronic rhinosinusitis: where do we stand today? *Allergy*. 2013;68:1-7.
33. Müller S, Marenholz I, Lee YA, Sengler C, Zitnik SE, Griffioen RW, Meglio P, Wahn U, Nickel R. Association of Filaggrin loss-of-function-mutations with atopic dermatitis and asthma in the Early Treatment of the Atopic Child (ETAC) population. *Pediatr Allergy Immunol*. 2009;20:358-361.
34. Enomoto H, Hirata K, Otsuka K, Kawai T, Takahashi T, Hirota T, Suzuki Y, Tamari M, Otsuka F, Fujieda S, Arinami T, Noguchi E. Filaggrin null mutations are associated with atopic dermatitis and elevated levels of IgE in the Japanese population: a family and case-control study. *J Hum Genet*. 2008;53:615-621.
35. Mackenzie KJ, Anderton SM, Schwarze J. Viral respiratory tract infections and asthma in early life; cause and effect? *Clin Exp Allergy*. 2014;44:9-19

36. Sigurs N, Aljassim F, Kjellman B, Robinson PD, Sigurbergsson F, Bjarnason R, Gustafsson PM. Asthma and allergy patterns over 18 years after severe RSV bronchiolitis in the first year of life. *Thorax*. 2010;65:1045-1052.
37. Jackson DJ, Gangnon RE, Evans MD, Roberg KA, Anderson EL, Pappas TE, Printz MC, Lee WM, Shult PA, Reisdorf E, Carlson-Dakes KT, Salazar LP, DaSilva DF, Tisler CJ, Gern JE, Lemanske RF Jr. Wheezing rhinovirus illnesses in early life predict asthma development in high-risk children. *Am J Respir Crit Care Med*. 2008;178:667-672.
38. Hedman L, Andersson M, Bjerg A, Forsberg B, Lundbäck B, Rönmark E. Environmental risk factors related to the incidence of wheeze and asthma in adolescence. *Clin Exp Allergy*. 2015;45:184-191.
39. Lee YL, Hsiue TR, Lee CH, Su HJ, Guo YL. Home exposures, parental atopy, and occurrence of asthma symptoms in adulthood in southern Taiwan. *Chest*. 2006;129:300-308.
40. Eriksson J, Ekerljung L, Lötvalld J, Pullerits T, Wennergren G, Rönmark E, Torén K, Lundbäck B. Growing up on a farm leads to lifelong protection against allergic rhinitis. *Allergy*. 2010;65:1397-403.
41. Campbell BE, Lodge CJ, Lowe AJ, Burgess JA, Matheson MC, Dharmage SC. Exposure to 'farming' and objective markers of atopy: a systematic review and meta-analysis. *Clin Exp Allergy*. 2015;45:744-757.

42. Lötval J, Ekerljung L, Lundbäck B. Multi-symptom asthma is closely related to nasal blockage, rhinorrhea and symptoms of chronic rhinosinusitis-evidence from the West Sweden Asthma Study. *Respir Res.* 2010;11:163.
43. Appleton SL, Adams RJ, Wilson DH, Taylor AW, Ruffin RE; North West Adelaide Health Study Team. Central obesity is associated with nonatopic but not atopic asthma in a representative population sample. *J Allergy Clin Immunol.* 2006;118:1284-1291.
44. Nieves A, Magnan A, Boniface S, Proud'hon H, Lanteaume A, Romanet S, Vervloet D, Godard P; ARIA. Phenotypes of asthma revisited upon the presence of atopy. *Respir Med.* 2005;99:347-354.
45. Knudsen TB, Thomsen SF, Nolte H, Backer V. A population-based clinical study of allergic and non-allergic asthma. *J Asthma.* 2009;46:91-94.
46. Chastang J, Baiz N, Parnet L, Cadwallader JS, De Blay F, Caillaud D, Charpin DA, Dwyer J, Lavaud F, Raheison C, Ibanez G, Annesi-Maesano I. Changes in body mass index during childhood and risk of various asthma phenotypes: a retrospective analysis. *Pediatr Allergy Immunol* 2017 (in press)
47. Ludviksdottir D, Diamant Z, Alving K, Bjermer L, Malinovschi A. Clinical aspects of using exhaled NO in asthma diagnosis and management. *Clin Respir J.* 2012;6:193-207.

48. Bjermer L, Alving K, Diamant Z, Magnussen H, Pavord I, Piacentini G, Price D, Roche N, Sastre J, Thomas M, Usmani O. Current evidence and future research needs for FeNO measurement in respiratory diseases. *Respir Med.* 2014;108:830-841.
49. Malinovschi A, Janson C, Högman M, Rolla G, Torén K, Norbäck D, Olin AC. Both allergic and nonallergic asthma are associated with increased FE(NO) levels, but only in never-smokers. *Allergy.* 2009;64:55-61.
50. Pekkanen J, Lampi J, Genuneit J, Hartikainen AL, Järvelin MR. Analyzing atopic and non-atopic asthma. *Eur J Epidemiol.* 2012;27:281-286.
51. Tomassen P1, Newson RB, Hoffmans R, Lötvald J, Cardell LO, Gunnbjörnsdóttir M, Thilsing T, Matricardi P, Krämer U, Makowska JS, Brozek G, Gjomarkaj M, Howarth P, Loureiro C, Toskala E, Fokkens W, Bachert C, Burney P, Jarvis D. Reliability of EP3OS symptom criteria and nasal endoscopy in the assessment of chronic rhinosinusitis--a GA² LEN study. *Allergy.* 2011 66:556-61

Table 1. Baseline characteristics

	Controls	Allergic asthma	P-value	Non-allergic asthma	P-value	P-value
	(n = 219)	(n = 410)	AA vs C	(n = 174)	NAA vs C	AA vs NAA
Age (mean±SD)	47.6 ±15.3	41.9 ±13.8	<0.001	50.3 ± 15.3	0.19	<0.001
Women (%)	50.2	56.5	0.13	61.5	0.03	0.26
BMI (kg/m ²) (mean±SD)	25.0 ±3.7	26.2 ±4.8	0.008	27.8 ± 5.32	<0.001	0.003
Smoking history (%)			0.55		0.06	0.004
Never smoked	56.6	57.1		44.8		
Ex-smoker	32.9	34.9		39.7		
Current smoker	10.5	8.0		15.5		
FEV1 (% pred) (mean±SD)(n = 756)	98.8 ± 13.6	92.9 ± 16.2	<0.001	87.8 ± 19.0	<0.001	0.004
FVC (% pred) (mean±SD) (n = 756)	106 ± 15.1	104 ± 15.6	0.25	101 ± 16.9	0.01	0.22
Total IgE (kU/L) (geometric mean (95% CI))(n = 705)	29 (23-35)	83 (72-95)	<0.001	28 (22-36)	>0.99	<0.001
FeNO, (ppb) (geometric mean (95% CI)) (n = 775)	16 (14-17)	21 (19- 22)	0.001	16 (15-18)	0.73	<0.001
PD20 (mg) (geometric mean (95% CI)) (n = 55)	-	1064 (373-3039)	-	315 (169-585)	0.06	0.01

(Body mass index (BMI), Forced expiratory volume in one second (FEV1), Forced vital capacity (FVC), Fraction of exhaled NO (FeNO), Cumulative dose of methacholine resulting in a 20% decrease in FEV1 (PD20))

Table 2. Upper airway symptoms, skin symptoms, and rhinoconjunctivitis in allergic and non-allergic asthma and controls expressed in percentages. P-value* adjusted for age, gender, BMI and smoking.

	Controls	Allergic asthma	P-value	Non-allergic asthma	P-value	P-value
	(n = 219)	(n = 410)	AA vs C	(n = 174)	NAA vs C	AA vs NAA
Allergic rhinitis (%)	23.3	82.3	<0.001	40.7	<0.001	<0.001
Rhinoconjunctivitis (%)	19.7	63.8	<0.001	31.0	0.01	<0.001
Non-infectious rhinitis (%)	40.4	90.5	<0.001	77.6	<0.001	<0.001
Chronic rhinosinusitis (%)	-	21.0	<0.001	19.5	-	0.16
Eczema (%)	47.0	72.3	<0.001	59.8	0.012	0.003
Itchy rash (%)	18.7	40.4	<0.001	34.1	0.001	0.16
Itchy rash last year (%)	12.8	30.2	<0.001	25.3	0.001	0.23

Table 3. Levels of total IgE and FeNO in relation to allergic rhinitis and itchy rash within the last 12 months

	Only asthma	+ rhinitis or rash	+ rhinitis and rash	p-value
Allergic asthma				
IgE (kU/L) (geometric mean (95% CI))	49 (33-74)	85 (72-100)	101 (75-135)	0.009
FeNO ppb (geometric mean (95% CI))	20 (16-26)	21 (20-23)	20 (17-22)	0.58
Non-allergic asthma				
IgE (kU/L) (geometric mean (95% CI))	33 (47-118)	23 (15-36)	31 (15-65)	0.37
FeNO ppb (geometric mean (95% CI))	15 (13-18)	16 (14-18)	22 (15-31)	0.10

(Fraction of exhaled NO (FeNO))

Table 4. Childhood risk factors for allergic and non-allergic asthma. Odds ratio (OR) (95% confidence interval (95% CI)), adjusted for age, gender body mass index and smoking

	Allergic asthma	Non-allergic asthma	P-value
	OR (95% CI)	OR (95% CI)	AA vs NA
Parental asthma	2.50 (1.73 - 3.60)	3.01 (2.01 -- 4.51)	0.29
Parental allergy	1.89 (1.42 - 2.52)	1.89 (1.36 -- 2.63)	>0.99
Day care < 5 yrs of age	1.19 (0.79 - 1.79)	1.71 (1.04 -- 2.81)	0.10
Shared bedroom < 5 yrs of age	1.18 (0.81 - 1.70)	1.49 (0.97 -- 2.30)	0.39
House pet < 1 yr of age	1.11 (0.76 - 1.63)	1.50 (0.97 -- 2.34)	0.13
Raised on a farm	0.98 (0.50 - 1.93)	2.29 (1.16 -- 4.53)	0.006*
Severe respiratory infection < 5 yrs of age	3.94 (2.11 - 7.35)	3.78 (1.91 -- 7.50)	0.87
Hospitalisation < 2 yrs of age	6.51 (1.94 - 21.8)	7.62 (2.10 -- 27.6)	0.65

Table 5. Assessment of mini-Asthma Quality of Life Questionnaire (AQLQ) scores for allergic and non-allergic asthma for the last two weeks. Scores from 1 to 7, with no impairment for score 7 (mean±standard deviation (SD)).

	Allergic asthma	Non-allergic asthma	P-value	P-value adjusted
Total AQLQ score (mean±SD)	6.0 ± 0.9	5.5 ± 1.1	<0.001	0.011
Symptoms (mean±SD)	5.8 ± 0.1	5.4 ± 1.2	<0.001	0.013
Activity limitation (mean±SD)	6.2 ± 1.1	5.8 ± 1.3	0.001	0.037
Emotional function (mean±SD)	6.1 ± 1.1	5.7 ± 1.2	0.002	0.073
Environmental stimuli (mean±SD)	6.0 ± 1.2	5.5 ± 1.3	<0.001	0.027

Fig 1

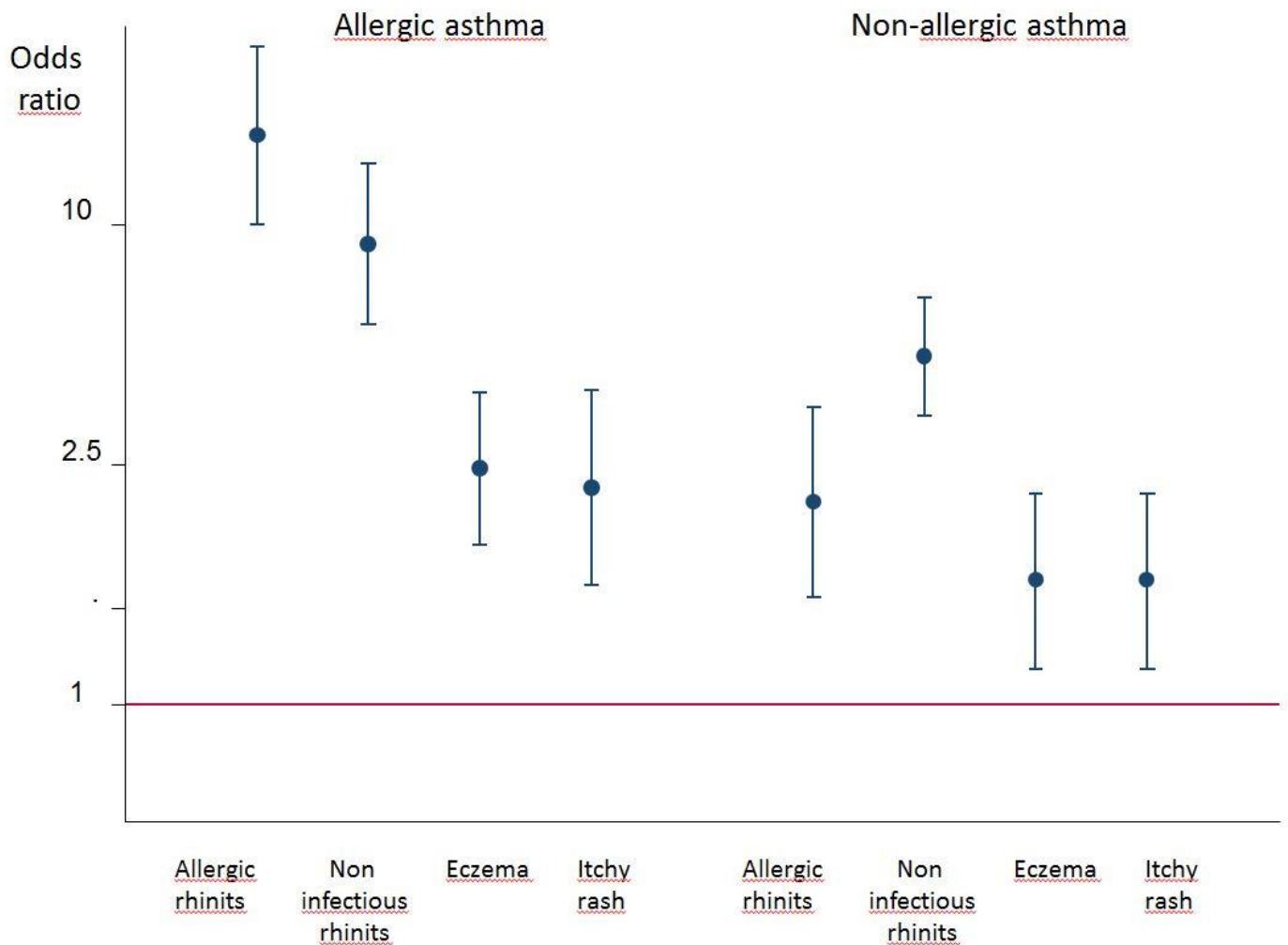


Figure 1 Independent association between allergic and non-allergic asthma and upper airway and skin disorders. The reference group comprised subjects without asthma and chronic rhinosinusitis (adjusted odds ratio (95% CI)). Adjustments were made for age, gender, smoking history and body mass index.

Fig 2

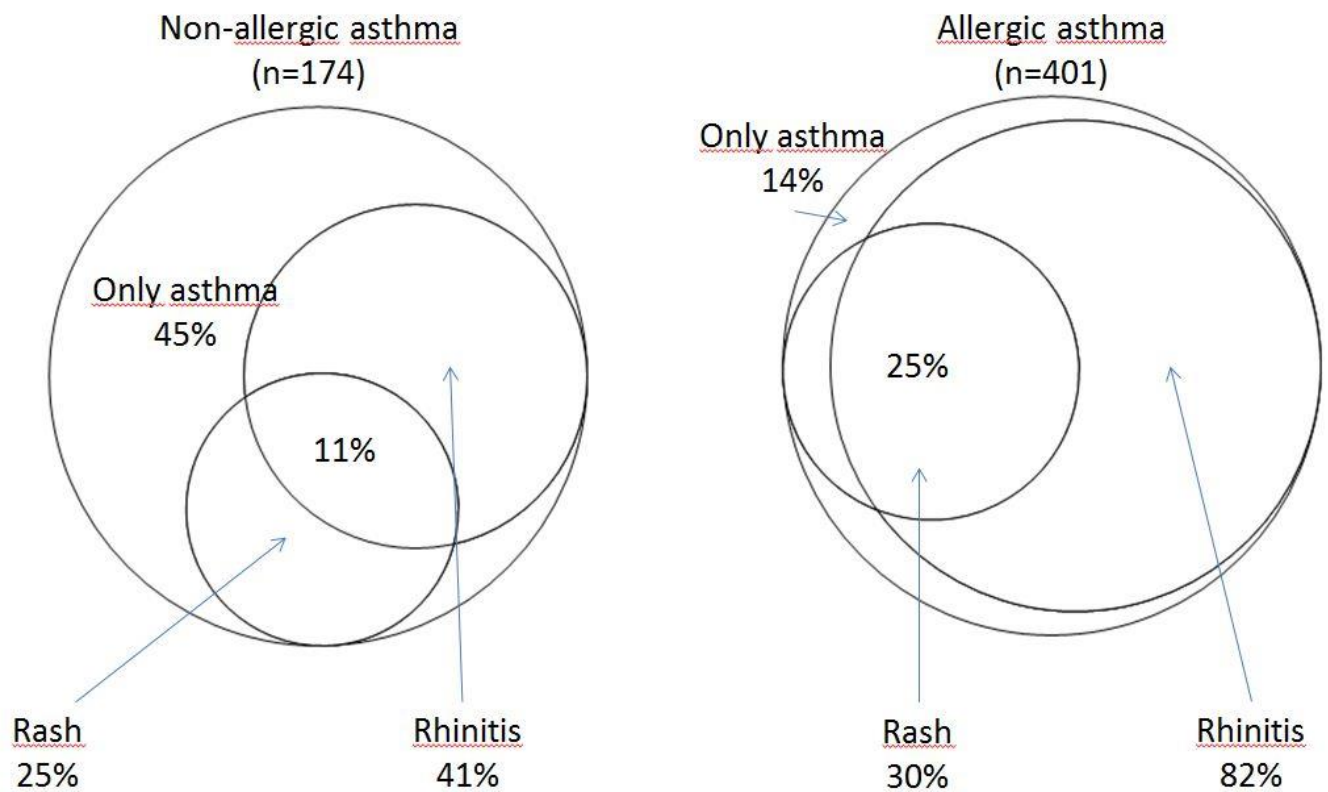


Figure 2. The co-existence of self-reported allergic rhinitis and itchy rash within the last 12 months in patients with allergic and non-allergic asthma. The prevalence of having only asthma and having all three disorders is marked.