Author: Maria Vosough
Supervisor: Christer Janson, Prof. MD.
Department of Medical science

Allergic and non-allergic asthma – Secondary analysis of the Swedish data from the GA$^2$LEN Survey
## Table of contents

Abbreviations: .................................................................................................................. 4  
Abstract .................................................................................................................................. 5  
Swedish summary / Populärvetenskaplig sammanfattning .................................................................. 6  
Background - Asthma and atopy ............................................................................................... 7  
  Asthma: ................................................................................................................................. 7  
  Figure 1, the direct and indirect pathways leading up to asthma symptoms ..................................... 8  
  Atopy: ................................................................................................................................... 8  
Background - Differences between allergic and non-allergic asthma .................................................. 9  
  Prevalence: ............................................................................................................................ 9  
  Inflammation / inflammatory markers: ....................................................................................... 9  
  Gender differences: .................................................................................................................. 11  
  Age differences: ..................................................................................................................... 12  
  Symptoms: ............................................................................................................................. 12  
  Severity: ................................................................................................................................ 13  
  Risk factors: ........................................................................................................................... 13  
  Response to medication: .......................................................................................................... 15  
  Comorbidity of atopic diseases: ............................................................................................... 16  
  Quality of life: ......................................................................................................................... 16  
  Aims: ..................................................................................................................................... 16  
  Hypothesis: ............................................................................................................................ 17  
Materials and methods .................................................................................................................. 18  
  Study population: ................................................................................................................... 18  
  Group allocation and Definitions: ............................................................................................. 18  
  Interviews and Clinical examinations: ........................................................................................ 19  
  The Mini Asthma Quality of Life Questionnaire: .......................................................................... 19  
  Ethics: .................................................................................................................................... 20  
  Statistical analyses: ................................................................................................................ 20  
Results ......................................................................................................................................... 21  
  Subject characteristics: ............................................................................................................. 21  
  Smoking: ................................................................................................................................. 21
Table 1, Subject characteristics
Table 2, Adjusted odds ratio
Clinical examinations:
Table 3, Lung function and inflammatory values
Symptoms:
Figure 2, Symptoms
Table 4, Symptoms of asthma
Atopic diseases:
Figure 3, Atopic diseases
Table 5, Atopic diseases
Risk factors during childhood:
Figure 4, Childhood risk factors
Table 6, Risk factors during childhood
Table 7, Adjusted odds ratio
Environmental factors:
Table 8, Impact of exposure to dampness, mould, gas, dust, smoke and subjects' educational level
Table 9, Adjusted odds ratio (OR) (95% CI). Adjusted for age, gender, BMI, smoking and educational level
Co morbidity:
Figure 5, Co morbidity
Table 10, Other diseases
Quality of life:
Figure 6, mAQLQ scores
Table 11, mAQLQ scores
Discussion
Conclusion
Reference list
Appendix
Abbreviations:

AMP = adenosine-5-9-monophosphate
AQLQ = Asthma Quality of Life Questionnaire
BHR = bronchial hyperresponsiveness
BMI = body mass index
COPD = chronic obstructive pulmonary disease
CRS = chronic rhinosinusitis
ENFUMOSA = European network for understanding mechanisms of severe asthma
EQ-5D = Euro Quality of Life Health Questionnaire
FEV1 = forced expiratory volume in one second
FeNO = fractional exhaled nitric oxide
FVC = forced vital capacity
GA\textsuperscript{2}LEN = Global Allergy and Asthma European Network
GOR = gastro oesophageal reflux
HRQL = health related quality of life
ICS = inhaled cortico-steroids
IgE = immunoglobulin E
IL-4/IL-5 = Interleukin 4/5
mAQLQ = mini Asthma Quality of Life Questionnaire
PEF = peak expiratory flow
PMA = perimenstrual aggravation of asthma
RAST = radioallergosorbent test
SPT = skin prick test
U-EPX = urinary eosinophil protein X
Abstract

Background: One very commonly used subgrouping for asthma is allergic and non-allergic. Both types of asthma share similarities but it has been shown in several studies that the two types have many important differences, for example; inflammatory response, cellular patterns, risk factors, gender differences and severity of disease. The aim of this paper is to further map these differences in order to understand the underlying mechanisms of asthma.

Materials and methods: This study is based on secondary analysis of previous collected data from the Global Allergy and Asthma European Network (GA²LEN) survey. We have used the Swedish cohort consisting of 575 individuals with asthma and 219 healthy controls. All participating individuals have responded to a postal survey and participated in an interview and clinical examination.

Results: We found significantly more cough and phlegm production in non-allergic asthma and more wheezing in allergic asthma. The allergic asthma group had a significantly higher frequency of other atopic diseases, but we also found that the non-allergic asthma group also significantly more often had other atopic diseases compared to the control group. The group with non-allergic asthma scored significantly lower on the quality of life questions compared to both those with allergic asthma and controls.

Conclusion: We have been able to show that the distribution of symptoms differs between the asthma groups. We have also found that early life events that affect the airways and certain environmental risk factors are important for the development of both asthma types, but particularly for the risk of developing non-allergic asthma. We have also further established the view of non-allergic asthma as an often more severe form of asthma shown in the lower ratings of the asthma related quality of life.
Swedish summary / Populärvetenskaplig sammanfattning

Astma är en sjukdom som drabbar lungorna och gör att man kan få svårt att andas ordentligt, drabbas av långvarig hosta och slem och lättare bli andfådd. Astma är mycket vanligt i Sverige och drabbar nästan 10 av befolkningen. Astma delas ofta upp i undergrupper och en mycket vanligt förkommande sådan är uppdelningen i allergisk och icke-allergisk astma (även kallat atopisk eller icke-atopisk astma). Allergisk astma betyder att man har både astma och för allergi samtidigt. De här två grupperna av astma har visats ha många likheter men det har i flera tidigare studier visats att astmatiker med samtidig allergi skiljer sig åt jämfört med icke-allergiska astmatiker på flera viktiga punkter. Målet med vår studie var att försöka tydliggöra dessa skillnader för att få en än mer fullständig bild av vad det är som orsakar astma, och vilka som ligger i riskzonen för att drabbas av astma.


Vi fann att de med icke-allergisk astma hade betydligt mer bekymmer med långvarig hosta och hosta med slem jämfört med dem med allergisk astma som i stället hade mer bekymmer med väsande andning (eng. wheezing). Personer med allergisk astma hade mycket oftare andra allergiska sjukdomar så som eksem och hösnuva jämfört med både de icke-allergiska astmatikerna och de friska kontrollerna. Men vi fann också att de med icke-allergisk astma också betydligt oftare hade de här andra allergiska sjukdomarna jämfört med de friska kontrollerna. Vi fann också att händelser tidigt i livet, så som allvarliga lunginflammationer eller infektioner som lett till sjukhusvård, är riskfaktorer för både allergisk och icke-allergisk astma, trots att den icke-allergiska astman oftast inte debuterar förrän långt senare i livet. De med icke-allergisk astma fick i genomsnitt mycket lägre värden på skattningen av livskvalité, vilket är ett tecken på att de lider mer av sin sjukdom.

Background - Asthma and atopy

Asthma:

Asthma is a chronic inflammatory disease of the airways that causes a varying airflow obstruction and remodeling of the respiratory system. The inflammation of asthma is associated with bronchial hyperresponsiveness (BHR) which leads to typical symptoms; coughing, wheezing, shortness of breath and chest tightness. These symptoms occur with and without exposure to a variety of stimuli [1].

Asthma is a very common disease, it occurs in about 10% of the adult population in most industrialized countries [1, 2]. Diagnosis of asthma is defined as a reversible airflow obstruction shown with spirometry. The diagnosis can often be determined on the clinical manifestations and the anamnesis, but the lung function should always be determined when there is a suspicion of asthma. A significant improvement of the forced expiratory volume in one second (FEV1) after inhalation of a bronchial dilator strongly supports the diagnosis. The presence of bronchial hyperresponsiveness (BHR) is a diagnostic criterion for asthma [3]. This means an increased sensitivity in the airways which leads to contraction of the bronchial smooth muscle when exposed to certain stimuli. This can be tested with for example methacholine or histamine inhalations which are known direct irritants for the airways. The mechanism responsible for BHR in asthma is unknown but the severity of BHR is correlated to the airway inflammation [4]. The airway inflammation in asthma is mainly mediated by polymorph infiltration of mast cells and eosinophil granulocytes [3]. The characteristic features of the inflammation are, besides leukocyte infiltration; epithelial sloughing, basement membrane thickening, edema and hyperplasia of mucus-secreting glands, and hypertrophy of bronchial smooth muscle [4]. A simple and non-invasive way of determining the expected amount of eosinophil granulocytes in the airways is to measure the amount of nitric oxide (FeNO) in the expiratory airflow [1]. This gives the physician a chance to monitor the ongoing inflammation in the airways in a patient with asthma. The chronic inflammation of a long lasting asthma will lead to remodeling of the airways; smooth muscle hypertrophy, increased vascularization, and subepithelial fibrosis. This can lead to an irreversible obstruction, much like that of chronic obstructive pulmonary disease (COPD) [3].

Asthma is often divided into different subtypes and one very commonly used subgrouping is allergic (or atopic/extrinsic) and non-allergic (or non-atopic/intrinsic) asthma. Both types of asthma share similarities but it has been shown in several studies that the two types have many important differences in for example; inflammatory response, cellular patterns, risk factors, gender differences and severity of disease [5].
The treatment of asthma is based on suppression of inflammation (inhaled cortico-steroids (ICS), sodium cromoglicate, anti-leucotriens) and bronchial dilatation (β2-agonists, anticholinergic drugs, theophylline, anti-leucotriens) [1].

Figure 1, the direct and indirect pathways leading up to asthma symptoms. Figure taken and translated from Intermedicin [1].

Atopy:

Atopy is a term referring to the predisposition to develop certain allergic hypersensitivity reactions. Being atopic therefore does not mean that the individual has to have a manifest allergy, but that they have reacted positively to for example a skin prick test (SPT) or that specific IgE antibodies have been found in a blood test [1].

There are several atopic diseases and they are commonly inherited together. Examples are hay fever (allergic rhinitis), eczema (atopic dermatitis), food hypersensitivity or allergic asthma. [1].
Background - Differences between allergic and non-allergic asthma

Prevalence:

Asthma has been increasing in prevalence during the end of the 20th century and today the estimate is that about 5-10% of the population of western countries has some form of asthma [2]. In the last decade however, the consensus is that asthma incidence has reached a plateau in the westernized countries, which some studies indicate could be due to a decrease in the allergic form of asthma [6, 7]. The prevalence of allergy in the population of western countries is considered to be about 30% [5]. Many studies have divided asthma into non-allergic and allergic, where those with allergic asthma show positive skin prick test (SPT) and increased levels of IgE in serum. It has been found that of all asthma about 70-80% is allergic and 20-30% (up to 40% in some studies) is non-allergic [8, 9]. As of now, we do not know if the individual with asthma and allergy have two different diseases - or if the two are in fact one combined disease, with different etiology, pathophysiology and symptoms compared to the non-allergic variant. But we can be certain that groups of individuals with allergic or non-allergic asthma differ in important ways and are relevant to separate in search for example mechanisms of pathiophysiology, optimal treatment, risk factors and heredity for subtypes of asthma.

Inflammation / inflammatory markers:

Allergic asthma has been extensively investigated and studied regarding the pathologic characteristics and considerably fewer studies have been made on the pathologic characteristics on non-allergic asthma. There are discussions going on whether allergic and non-allergic individuals with asthma have two distinct different inflammatory diseases. The studies that have compared the inflammatory responses in allergic and non-allergic asthma have had results showing similarities but also significant differences in these two conditions [5, 10].

The differences reported are for example those with allergic asthma have a higher concentration of exhaled nitric oxide (FeNO) compared to those with non-allergic asthma, which have FeNO values on the same level as healthy individuals [11, 12]. No correlation has been found between the amount of exhaled nitric oxide and lung function values, peak expiratory flow or symptom score in non-allergic asthma, allergic asthma or in healthy controls [11]. There has, however, been found a correlation between FeNO and airway hyperresponsiveness to methacholine, where those with allergic, but not non-allergic, asthma have a correlation between FeNO and the dose-response slope for methacholine.
This suggests that elevated NO levels, or the mechanisms leading to its increase, may contribute to airway hyperresponsiveness.

A clear connection has been found between high levels of FeNO and high eosinophilic levels in both blood and sputum [13]. Allergic asthma have several times been found to have higher value of FeNO and higher level of eosinophils in serum [11, 14]. Amin et al. has shown those with allergic asthma have higher levels of eosinophil granulocytes in bronchial biopsies than those with non-allergic asthma [15]. Both allergic and non-allergic asthma have increased levels compared to healthy individuals. Both groups also have been shown to have increased levels of mast cells compared to healthy individuals. Mast cells uniquely populate all vascularized organs and tissues, including the upper and lower respiratory tree, even in healthy individuals. However, the distribution of mast cells in the bronchial mucosa differs between allergic and non-allergic asthma, with mast cells being accumulated in the smooth muscle compartment to a higher extent in patients with allergic asthma than in those with non-allergic asthma [16]. Mast cells in allergic asthma also showed more general signs of activation, than in non-allergic asthma. This could likely relate to increased BHR and smooth muscle hyperplasia in those with allergic asthma [17]. The levels of neutrophil granulocytes have been shown to be increased in those with non-allergic asthma but not for those with allergic asthma [18]. It has been suggested that high levels of neutrophils is rather a marker of severe asthma than of non-allergic asthma, and that neutrophils is part of the pathophysiology of irreversible airflow obstruction [19].

Furthermore, the number of T-lymphocytes has been shown to be higher in those with allergic asthma compared to those with non-allergic asthma [15]. The cytokines Interleukin-4 (IL-4) and IL-5, which triggers the B- and T-cell response, are also more frequently found in those with allergic asthma, although there have been studies with results of similar increase in IL-4 and IL-5 for both those with allergic and non-allergic asthma [20].

It is widely known that total IgE levels in serum are above normal in those with allergic asthma and that serum IgE is a hallmark of allergy. However, Beeh et al. has shown that elevation of serum IgE is observed also in those with non-allergic asthma compared to healthy individuals. The study showed that higher levels of serum total IgE in those with non-allergic asthma are associated with a more severe airway obstruction and BHR, thus representing a more severe subtype of asthma [21].

Bronchial irritating agents are divided into those with direct effect, such as methacholine, and those with an indirect effect, such as cold air and adenosine-5'-9-monophosphate (AMP). The direct effect comes from the contraction of the smooth muscle that causes the airways to narrow, and the indirect effect comes from inflammatory cells that releases mediators that causes the airways to narrow. Because the indirect effect, by for example AMP, is
dependent on inflammatory cells it has been suggested that it better shows the underlying airway inflammation and not just the airway hyperresponsiveness that the direct effect does. Those with allergic asthma are more hyperresponsive to inhaled AMP than those with non-allergic asthma [22]. Both asthma groups have the same reaction to methacholine and cold air [22].

The degree of epithelial damage has in one study been shown to be significantly higher in those with allergic asthma than in those with non-allergic asthma [15]. The layers of the extracellular matrix protein Tenascin of the basal membrane and the basal lamina protein Laminin are significantly thicker in those with allergic asthma compared to those with non-allergic asthma. Tenascin is normally only expressed during embryonic development, oncogenesis and tissue repair. The bronchial epithelial damage has been shown to correlate with the levels of eosinophils, and the thickness of the layers of Tenascin and Laminin correlates with the number of mast cells [15, 23].

**Gender differences:**

The gender difference in asthma incidence has been shown to be very age-dependent. In children and teenagers the prevalence of asthma is higher in boys than in girls and allergic asthma is dominant [24]. Children with severe asthma have no gender bias, however, and are more often allergic, but still with relatively well preserved lung function [25]. Between ages 20 to 35 years there has not been found any gender difference in prevalence but after 35 years of age women have about 20% higher relative risk of asthma than men of the same age, and non-allergic asthma is the dominant form. Even though the total incidence of asthma differs a lot between countries, the same results of gender difference have been found over large geographical areas [24]. This is the same as for other atopic diseases; such as rhinitis and eczema (atopic dermatitis) [8]. The prevalence of non-allergic asthma seems to increase with age, but even in children and teenagers the prevalence of non-allergic asthma is higher in girls than in boys. Underdiagnosis of asthma appears to be more common for non-allergic individuals, but as frequent in women as in men [8].

In trying to find the reason to why women have a higher risk for developing non-allergic asthma, when over 35 years of age, a higher exposure (occupational or domestic) to bronchial irritants in women or a greater susceptibility in women than men to bronchial irritants may contribute. The latter may to some extent be related to women’s lower airway calibre. However, women have also been shown to have increased risk of BHR, which remain after adjustment for gender differences in airway calibre [24].

The role of sex-hormones in the prevalence of asthma is not fully investigated or understood as of yet but is a frequently suggested theory for partially explaining the gender differences [24]. Perimenstrual aggravation of asthma (PMA) with an increase in symptoms and a significant decline in PEF values has been reported in 30–40% of women, and has been shown to be independent of presence or absence of allergy [9]. It has also been shown that
hormone replacement therapy (HRT) during menopause improves asthma symptoms, but contrastingly there has also been research showing that postmenopausal women using HRT have an even higher risk of developing asthma than women who doesn’t. A possible explanation for these discrepant findings could be that the effects of HRT differ in subgroups of women [9]

**Age differences:**

Non-allergic asthma is commonly seen as a disease that has later onset than allergic asthma. However, some studies indicate that non-allergic asthma is more common in children than what is previously known [26-28]. But still, allergic asthma is in total more common at a younger age than non-allergic asthma in the western world [5].

Ulrik et. al. has shown that “outgrowing” asthma may occur more commonly in children with mild or infrequent symptoms compared to those with severe symptoms [29]. However, many of those children who had ceased wheezing when reaching adulthood had still increased bronchial responsiveness to inhaled irritants (such as histamine), suggesting that the disease might only be quiescent and not fully healed. In children with moderate to severe asthma, “outgrowing” asthma appears to be the exception rather than the rule. For children with non-allergic asthma, increasing age at the onset of respiratory symptoms leads to a more favorable outcome whereas no such relation has been found in children with allergic asthma [29].

Unfortunately, asthma has been found to commonly be misdiagnosed as COPD in individuals of higher age [30], which often means inadequate medication and management of elderly with asthma.

**Symptoms:**

Seasonal asthma or seasonal increases of asthma symptoms are more frequent in those with allergic asthma than in those with non-allergic asthma [5]. Exercise-induced asthma has been found to be more common in allergic asthma. Cough and dyspnea as a symptom of asthma has been found to be more frequent in those with non-allergic asthma and wheezing has in some studies been found to be more frequent in those with allergic asthma [31], but other studies found wheezing to be equally common in these asthma subtypes [5]. Asthma patients with persistent severe asthma have been recorded to more often be in the older age range, to more likely have persistent productive cough and to have higher total IgE levels [32].
Severity:

Several clinical studies indicate that non-allergic asthma may be more severe and difficult to control than allergic asthma because of the reported more severe airway obstruction and BHR [5, 18]. FEV1 and FVC values have in some studies been shown to be lower in those with non-allergic asthma, and the prognosis regarding lung function decline is considered to be worse for these individuals [29]. However, many of the studies on non-allergic asthma have only been done on patients with severe asthma and less is therefore known on the non-allergic asthma in the general population [9, 24]. It has also been found that individuals with mild asthma are more often not diagnosed and hence not recognized as asthmatics by their physician.

There is a European network for understanding mechanisms of severe asthma (ENFUMOSA). In one of their studies they found that positive outcomes of different markers of allergy showed inverse relation to asthma severity, indicating that allergic asthma is more often less severe [18]. They also found that patients with severe asthma were less likely to be skin prick positive, meaning non-allergic, and more likely to have high levels of neutrophils in sputum than patients with less severe asthma. But as mentioned above, it has been suggested that high levels of neutrophils may in fact be a marker of severe asthma. The authors of this study even inclined that severe asthma may in fact be a different form of asthma, rather than an increase in asthma symptoms.

Risk factors:

Body mass index:

Firstly, there are risk factors common for both groups and one of them is body mass index (BMI). Several studies have shown that both those with allergic and non-allergic asthma have higher BMI than healthy controls. This has been shown to be true in both children and adults [26, 33]. However, Appleton et al. showed that central obesity (measured in waist circumference) was only significantly associated with increased risk of non-allergic asthma [34]. Despite many studies on the subject, the ultimate cause of the relationship between high BMI and asthma has not been identified. A suggested explanation for the relation between obesity and asthma may be the presence of a low-grade systemic inflammation in obese individuals, with increased levels of pro-inflammatory cytokines and mediators that would lower the threshold for developing asthma [35]. In addition, the systemic inflammation that is present in obesity may cause insulin resistance. Thuesen et al. showed that insulin resistance is an even stronger predictor for the development of adult-onset asthma than the presence of obesity [36].
Contrastingly there are data showing that asthma may be overdiagnosed in obese patients. Sin et al. found that obesity was a risk factor for self-reported asthma, bronchodilator use and dyspnoea, but also that the obese group in the study had the lowest risk for significant airway obstruction [37]. Schachter et al. found that even though moderate and severe obesity was a risk factor for asthma and wheeze; the severity of airway obstruction and airway hyperresponsiveness was not higher in the obese [38]. It has been found that gastrooesophageal reflux (GOR) is more common in both individuals with high BMI and individuals with asthma, and that antireflux treatment can in fact reduce asthma symptoms. Gunnbjornsdottir et al. found GOR to be an independent risk factor for onset of wheeze and asthma [33].

**Smoking:**
Smoking, both passive, previous and current, has been shown to be an important risk factor for non-allergic asthma, whereas no association has been found for allergic asthma [8, 29, 39]. Active smoking has been shown to decrease lung function for those with non-allergic asthma but not for those with allergic asthma. Nieves et al. found a larger amount of those with non-allergic asthma than those with allergic asthma to be current or previous smokers [5], but others haven’t found any difference in prevalence or intensity between the two groups [39].

**Air quality:**
There are studies showing an increased prevalence of respiratory symptoms in children and adults living in damp homes, with essentially no difference between allergic and non-allergic asthma [27, 40]. For non-allergic asthma, indoor air quality has been found to be an important risk factor (for example; passive smoking), while for allergic asthma the association is not as strong [26, 27, 41]. McCormack et al. found in a study on children living in city areas that high concentration of in-house particle matter was associated with worsening of asthma symptoms for both children with allergic and non-allergic asthma [42].

**Exercise:**
Exercise-induced asthma has been shown to be more frequent in those with allergic asthma, but as this group of patients is younger they might have more exercise practice and therefore more often notice the worsening of asthma symptoms [5]. Still, exercise induced asthma has been found in up to 40% of those with non-allergic asthma, so the difference of risk is not great.

**Educational level of parents:**
Children from highly educated parents have been found to have a certain protection from non-allergic respiratory symptoms [41]. This is believed to be due to a lower rate of household smoking and a higher rate of breastfeeding. But instead these children of highly
educated parents are more frequently sensitized to common indoor allergens, and therefore might be more prone to allergic asthma.

*Early life events:*  
Non-allergic asthma, but not allergic asthma, have been found to be associated with certain early-life events such as frequent otitis and croup and also with environmental exposures such as building dampness and unsatisfactory school cleaning [26]. Breastfeeding less than 3 months has been found to be a significant risk factor for non-allergic asthma, but has shown no significance for allergic asthma [27].

*Heredity:*  
Both allergic and non-allergic asthma are associated with parental asthma, which is a well-established fact. However, for allergic asthma a familial history of asthma is probably the most important risk factor, significantly more important than for non-allergic asthma [13, 14, 25].

*Pets:*  
The effect of pet-keeping in relation to allergy and asthma has been much debated, with many studies showing diverging results. Studies have shown that the effects varies between the type of pet and of the community prevalence of that pet [43]. For example, cats owned in childhood were associated with more allergic, but not non-allergic asthma, in areas with low community prevalence of cats. Both Janson et al. and Svanes et al., has reported that owning a dog in childhood seems to protect against adult allergic asthma, but seemingly increases the risk for non-allergic asthma instead [26, 43]. Fretzayas et al. has done a thorough review on the available studies on the subject and states that further appropriately designed birth cohort studies are needed to explore whether exposure to allergens from pets promotes or protects from the development of atopy and asthma [44].

*Country of birth:*  
Studying immigration has shown that the risk of asthma is the same as of the country of birth if the child moves to a different country only after the age of 4 years, which means that if you immigrate before the age of 4 you will have the same risk as of those native to the new country [25].

*Response to medication:*  
Although therapy, if used according to management guidelines, controls the disease in the majority of patients, it has been found that a subgroup of asthmatics show reduced responsiveness to the standard therapy and experience greater morbidity than those with asthma whose disease is adequately controlled by therapy [45]. This group also scores lower
on quality of life questionnaires. These patients with more severe asthma account for approximately 5-10% of the asthmatic population [45]. The asthma patients taking regular oral corticosteroids have been observed to have increased excretion of NO in exhaled air, which is further evidence of persistent airway inflammation and also a possible marker of relative resistance to steroid treatment [18]. Another hypothesis emerging from the ENFUMOSA study [18] is that severe asthma might be characterized by a diminished sensitivity to corticosteroids. No difference has been found specifically between allergic and non-allergic asthma. But the biggest problem in so called failed response to medication has been found to be related to lacking patient compliance [45].

Comorbidity of atopic diseases:

Rhinitis and asthma have been shown in several studies to be closely linked; 20–50% of patients suffering from rhinitis are also diagnosed with asthma and the presence of rhinitis has been shown occur in up to 80% of patients with asthma [30]. Rhinitis is more frequent in those with allergic asthma and especially for those with a familial history of rhinitis, current rhinitis and seasonal rhinitis or seasonal increase of symptoms of rhinitis [5]. Conjunctivitis and eczema (atopic dermatitis) are also more frequent in those with allergic asthma than in those with non-allergic asthma, although the difference has only been shown to be significant for conjunctivitis. Familial eczema is the dominating form. This makes it clear that atopic diseases are often inherited together [5].

Quality of life:

Well-being and functioning have been found to be negatively associated with the presence of asthma [30]. Female asthmatic patients report more symptoms and poorer health related quality of life (HRQL) than male patients, but these differences cannot be fully explained by disease severity. Ehrs et al. found in a study of mild asthma that the quality-of-life scores (using the Asthma Quality of Life Questionnaire) were generally higher in those with allergic asthma than in those with non-allergic asthma [12], and a recent study by Ek et al. showed that impaired quality of life was independently associated with having a negative SPT (meaning non-allergic asthma) as well as lower lung function, obesity, high age, current smoking and comorbid chronic rhinosinusitis (CRS) [46].

Aims:
The aim of this study is to find out if there are significant differences between allergic asthma and non-allergic asthma in Sweden regarding symptoms of asthma, inflammatory
markers, risk factors, life style (smoking, education etc.), environmental factors and quality of life.

Hypothesis:
The hypothesis is that there are significant differences between these two asthma subgroups and it is therefore relevant to separate them clinically in order to provide the best and most effective health care.
Materials and methods

Study population:

The current study is a secondary analysis of the Swedish data from the GA\textsuperscript{2}LEN-survey and no new data has been added.

The GA\textsuperscript{2}LEN-survey was conducted in 19 European centers between year 2008 and 2010. A symptom-based questionnaire on asthma, rhinitis and CRS was distributed to a random population-based sample [47]. Among those who responded randomly selected subgroups was invited for a clinical follow-up. The subgroups consisted of individuals with either asthma or CRS, both asthma and CRS, or neither asthma nor CRS (healthy control group). In Sweden, 27 866 persons responded to the postal survey in 2008, of whom 1329 persons participated in the follow-up during 2009 and 2010. Four Swedish centers; Gothenburg, Stockholm, Uppsala and Umeå, participated in the postal survey and follow-up interview. The age range of the participants was 17-76 years. The Swedish cohort has been described elsewhere [7]. In the present study only 794 of the participants from the Swedish cohort has been analyzed.

Group allocation and Definitions:

In the GA\textsuperscript{2}LEN study patient characterization was based on the follow-up interview. Asthma was defined as self-reported diagnosis of asthma and either asthma symptoms or asthma treatment. Symptoms were defined as wheezing, and/or attacks of shortness of breath, and/or awakening at night with breathlessness in the previous 12 months and asthma treatment were defined as taking any asthma medication during the last 12 months. CRS was defined following the European Position Paper on Rhinosinusitis and Nasal Polyps’ (EP\textsubscript{3}OS) criteria [48], which means that the presence of at least two of the following symptoms for at least 12 weeks in the past year: nasal blockage, nasal discharge, facial pain or pressure, reduction in sense of smell (with at least one of the symptoms being nasal blockage or nasal discharge).

Subjects who were not classified as having asthma or CRS neither in the first postal survey nor in the follow up interview and who did not report attacks of shortness of breath, wheezing, use of asthma medicines or CRS symptoms constituted the control group.

Subjects who did not completely fulfill the criteria for any of the groups above (n=388) were not included in the follow up.
In the present study three new groups were created from the data previously collected; those with asthma (criteria as listed above) and negative skin prick test (SPT) constituted the non-allergic asthma group, those with asthma and positive SPT constituted the allergic asthma group and those with no asthma regardless of atopic status constituted the control group. The non-allergic asthma group consisted of 174 individuals, the allergic asthma group of 401 individuals and the control group of 219 individuals. No regard has been taken to if subjects have CRS or not in creation of these new groups for the present study.

**Interviews and Clinical examinations:**

In the follow up subjects were invited for both interviews and clinical examinations. The interviews included questions of symptoms of asthma, symptoms of atopic disease, previous and present smoking, current use of medication, medical history, etc.

The clinical examination included the following:

**Skin prick test:** SPT was performed on the inside of the forearm using a standard set of allergens standardized for the GA\(^2\)LEN network including timothy grass, mixed grass, *Dermatophagoides pteronyssinus*, cat, birch, blattella, olive, *Alternaria*, dog, *Artemisia*, *Parietaria, Dermatophagoides farinae*, histamine (positive control) and diluent (histamine control). A positive SPT was defined as a weal at least 3 mm at the widest diameter.

**Atopy/allergy** was defined as the presence of at least one positive SPT finding. Those individuals with a positive SPT finding were included in the allergic asthma group in the present study, if they also fulfilled the asthma criteria.

**Exhaled NO:** Nitric oxide in exhaled air was assessed using NIOX MINO (NIOX MINO®; Aerocrine, Stockholm, Sweden) according to the American Thoracic Society’s (ATS) and European Respiratory Society’s (ERS) recommendations [49].

**Spirometry:** Lung function measurement was performed using the EasyOne™ Spirometer (ndd Medizintechnik AG) according to the ATS spirometry standards [50]. Forced vital capacity (FVC) and forced expiratory volume in one second (FEV\(_1\)) were registered before and after bronchodilatation (inhalaion of 200 µg salbutamol, a short-acting β\(_2\)-adrenergic receptor agonist). The equations from the European Community for Steel and Coal (ECSC) were used as reference values for calculation of lung function [51].

**The Mini Asthma Quality of Life Questionnaire:**

In the follow up the participants who fulfilled the asthma criteria in the original postal survey also filled out the Mini Asthma Quality of Life Questionnaire (mAQLQ) by Juniper [52]. mAQLQ is a short version of the Asthma Quality of Life Questionnaire (AQLQ), assessing the
impact of asthma on quality of life. The questionnaire consists of 15 questions, divided into 4 domains: symptoms; activity limitations; emotional functions and effects of environmental stimuli. Each domain is scored from 1 to 7, where 1 indicates maximal impairment and 7 no impairment. The overall score is the mean value based on all questions.

**Ethics:**

The study was approved by the Regional Ethical Review Board in Stockholm, Sweden (Dnr 2008/1100-31/4), and the collected personal data was treated according to the Swedish personal data act.

**Statistical analyses:**

All analyses were performed using STATA 12 (STATA Corp, Texas, USA). The results are given as mean or geometric mean value and 95% confidence interval (CI). FeNO was log-transformed and used for further analysis. The differences between groups were either tested using a χ2-test or an analysis of variance (ANOVA) with the Bonferroni correction for multiple-comparisons. Multiple nominal and binominal logistic regressions were used in the multivariate analyses. A P-value <0.05 was considered significant.
Results

Subject characteristics:

The non-allergic asthma group consisted of 174 persons and the allergic asthma group of 401 persons, which means that 30.3% had non-allergic asthma and 69.7% has allergic asthma in the current study. The allergic asthma group was significantly younger compared to the non-allergic and control group (Table 1). There were more women in the non-allergic asthma group than in the allergic asthma and control groups, but the difference was only statistically significant between controls and non-allergic asthma. The relative risk of having non-allergic asthma was significantly increased for women, the same was not true for allergic asthma (Table 2). The mean value of BMI was significantly higher in subjects with asthma compared to the control group, but there was also a significant difference with higher mean values of BMI in those with non-allergic asthma compared to the allergic asthma group. The relative risk of both kinds of asthma increases with higher BMI but the risk is highest for non-allergic asthma. There was a significant difference in the reported age of first asthma attack, where those with allergic asthma was much younger than those with non-allergic asthma, with a mean difference of over 10 years.

Smoking:

To ever have smoked regularly for more than one year was significantly more common in the non-allergic asthma group compared to both the allergic asthma and control groups (Figure 2, Table 1). Current smoking was more common in the non-allergic asthma group compared to the allergic asthma group. There was no significant difference between the allergic asthma group and the control group regarding smoking prevalence.

Table 1, Subject characteristics. 
Age, sex distribution, body mass index (BMI), age of asthma debut and smoking history (%).

<table>
<thead>
<tr>
<th></th>
<th>Control (n219)</th>
<th>Non-allergic asthma (n174)</th>
<th>P-value*</th>
<th>Allergic asthma (n401)</th>
<th>P-value*</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>47.6 ± 15.3</td>
<td>50.3 ± 15.3</td>
<td>0.20</td>
<td>41.9 ±13.8</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Women</td>
<td>50.2</td>
<td>61.5</td>
<td>0.03</td>
<td>56.5</td>
<td>0.13</td>
<td>0.26</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.0 ± 3.69</td>
<td>27.8 ± 5.32</td>
<td>&lt;0.001</td>
<td>26.2 ± 4.84</td>
<td>0.006</td>
<td>0.002</td>
</tr>
<tr>
<td>Age of first asthma attack</td>
<td>-</td>
<td>30.4 ± 1.43</td>
<td>-</td>
<td>17.8 ± 0.736</td>
<td>-</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ever smoked &gt;1y</td>
<td>42.9</td>
<td>55.2</td>
<td>0.016</td>
<td>42.9</td>
<td>1.0</td>
<td>0.007</td>
</tr>
<tr>
<td>Never smoker</td>
<td>56.6</td>
<td>44.8</td>
<td>57.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>32.9</td>
<td>39.7</td>
<td>34.9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoking</td>
<td>10.5</td>
<td>15.5</td>
<td>0.14</td>
<td>8.0</td>
<td>0.29</td>
<td>0.006</td>
</tr>
</tbody>
</table>
Table 2, Adjusted odds ratio (OR) for subject characteristics (95% CI).

*Adjusted for age, gender, BMI and smoking.*

<table>
<thead>
<tr>
<th></th>
<th>Non-allergic asthma</th>
<th>Allergic asthma</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age per 10yrs</td>
<td>1.03 (0.89-1.20)</td>
<td>0.69 (0.61-0.79)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Women</td>
<td>1.75 (1.14-2.65)</td>
<td>1.31 (0.93-1.85)</td>
<td>0.14</td>
</tr>
<tr>
<td>BMI per 5units</td>
<td>1.92 (1.51-2.46)</td>
<td>1.66 (1.33-2.07)</td>
<td>0.12</td>
</tr>
<tr>
<td>Never smoked</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Ex smoker</td>
<td>1.26 (0.78-2.01)</td>
<td>1.37 (0.92-2.03)</td>
<td>0.70</td>
</tr>
<tr>
<td>Current smoking</td>
<td>1.50 (0.78-2.87)</td>
<td>0.76 (0.41-1.40)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

P-value = between NAA and AA

Clinical examinations:

Lung function (FEV1 and FVC) was impaired both in subjects with allergic asthma and non-allergic asthma compared to the control group (Figure 3, table 3). The non-allergic asthma group had significantly worse FEV1 than the allergic asthma group, but this difference was no longer significant after adjusting for age, gender, BMI and smoking. A ratio of FEV1/VC less than 0.70 was significantly more common for those with non-allergic asthma compared to those with allergic asthma, also after adjusting for age, gender, BMI and smoking. 32.5% of those with non-allergic asthma had a FEV1/VC ratio below 0.70. The FeNO and total IgE levels were significantly higher in the allergic asthma group compared to both the non-allergic asthma group and controls, no difference was found between the two latter groups.

Table 3, Lung function and inflammatory values (SD)

<table>
<thead>
<tr>
<th></th>
<th>Control (n219)</th>
<th>Non-allergic asthma (n147)</th>
<th>P-value*</th>
<th>Allergic asthma (n401)</th>
<th>P-value*</th>
<th>P-value*</th>
<th>P-value*</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1</td>
<td>98.8 ± 13.6</td>
<td>87.8 ± 19.0</td>
<td>&lt;0.001</td>
<td>92.9 ± 16.2</td>
<td>&lt;0.001</td>
<td>0.003</td>
<td>0.72</td>
<td></td>
</tr>
<tr>
<td>FVC</td>
<td>106 ± 15.1</td>
<td>101 ± 16.9</td>
<td>0.01</td>
<td>104 ± 15.6</td>
<td>0.29</td>
<td>0.24</td>
<td>0.10</td>
<td></td>
</tr>
<tr>
<td>FEV1/VC &lt;0.70</td>
<td>8.5</td>
<td>32.5</td>
<td>&lt;0.001</td>
<td>14.1</td>
<td>0.04</td>
<td>&lt;0.001</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>FeNO</td>
<td>15.5 (14.3-16.9)</td>
<td>16.4 (14.9-18.0)</td>
<td>1</td>
<td>20.7 (19.4-22.1)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Total IgE</td>
<td>28.6 (23.5-34.8)</td>
<td>27.9 (21.7-35.9)</td>
<td>1</td>
<td>82.8 (72.3-94.9)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

P-value* = between control/NAA, P-value* = between control/AA, P-value* = between NAA/AA, P* = P-value between NAA/AA, adjusted for age, gender, BMI and smoking
Symptoms:

Regarding symptoms of asthma, the results show that those with non-allergic asthma have an overall worse situation of symptoms compared to those with allergic asthma, with significant differences for daytime and nocturnal cough attacks and morning and daytime phlegm cough (Figure 4, table 4). Wheeze was more common in the allergic asthma group. All these differences, except nocturnal cough attacks, remained significant after adjusting for age, gender, BMI and smoking. We didn’t find any significant differences between the asthma groups regarding the use of asthma medication or having any asthma attacks in the last year or in the number of attacks in the last year.

Figure 2, Symptom distribution for allergic and non-allergic asthma (%).

*Significant difference (P < 0.05) between NAA and AA, after adjusting for age, gender, BMI and smoking
Atopic diseases:

Allergic rhinitis, rhinitis without having a cold and rhinoconjunctivitis all had very significant P-values between all three groups, showing that these atopic diseases were most frequent in the allergic asthma group but also significantly more frequent in the non-allergic asthma group compared to the control group (Figure 5, table 5). These differences remained significant after adjusting for age, gender, BMI and smoking. CRS did not differ in frequency between the asthma groups. To ever have suffered from eczema was significantly more common in the allergic asthma group compared to the non-allergic asthma and control groups, but it was also significantly more common in the non-allergic asthma group compared to the controls. Ever having chronic itching rashes or rashes during the last 12 months did not show any difference between the asthma groups but was significantly more common for those with asthma compared to the controls. To ever have had any food hypersensitivity was more frequent in the allergic asthma group compared to the non-allergic asthma and the control groups, but it was also significantly more common amongst those with non-allergic asthma compared to the controls. Adjusting for age, gender, BMI and smoking did not change the outcomes of these results.
Allergic and non-allergic asthma

– Secondary analysis of the Swedish data from the GA²LEN Survey

Figure 3, Atopic diseases (%).

Table 5, Prevalence of atopic diseases for allergic asthma, non-allergic asthma and controls (%)

<table>
<thead>
<tr>
<th></th>
<th>Control (n219)</th>
<th>Non-allergic asthma (n174)</th>
<th>P-value 1</th>
<th>Allergic asthma (n401)</th>
<th>P-value 2</th>
<th>P-value 3</th>
<th>P *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergic rhinitis</td>
<td>23.3</td>
<td>40.7</td>
<td>&lt;0.001</td>
<td>82.3</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Rhinitis, no cold</td>
<td>40.4</td>
<td>77.6</td>
<td>&lt;0.001</td>
<td>90.5</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Rhinitis &gt;12m</td>
<td>33.8</td>
<td>69.9</td>
<td>&lt;0.001</td>
<td>82.5</td>
<td>&lt;0.001</td>
<td>0.001</td>
<td>0.010</td>
</tr>
<tr>
<td>Rhinoconjunctivitis &gt;12m</td>
<td>19.7</td>
<td>31.0</td>
<td>0.01</td>
<td>63.8</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CRS</td>
<td>0.0</td>
<td>19.5</td>
<td>&lt;0.001</td>
<td>21.0</td>
<td>&lt;0.001</td>
<td>0.16</td>
<td>0.14</td>
</tr>
<tr>
<td>Ever eczema</td>
<td>47.0</td>
<td>59.8</td>
<td>0.012</td>
<td>72.3</td>
<td>&lt;0.001</td>
<td>0.003</td>
<td>0.010</td>
</tr>
<tr>
<td>Ever chronic itching rashes &gt;6m</td>
<td>18.7</td>
<td>34.1</td>
<td>0.001</td>
<td>40.4</td>
<td>&lt;0.001</td>
<td>0.16</td>
<td>0.22</td>
</tr>
<tr>
<td>Rashes &gt;12m</td>
<td>12.8</td>
<td>25.3</td>
<td>0.001</td>
<td>30.2</td>
<td>&lt;0.001</td>
<td>0.23</td>
<td>0.25</td>
</tr>
<tr>
<td>Ever food hypersensitivity</td>
<td>19.3</td>
<td>38.0</td>
<td>&lt;0.001</td>
<td>52.8</td>
<td>&lt;0.001</td>
<td>0.001</td>
<td>0.02</td>
</tr>
</tbody>
</table>

P-value 1 = between control/NAA, P-value 2 = between control/AA, P-value 3 = between NAA/A, P* = P-value between NAA/AA, adjusted for age, gender, BMI and smoking

*)Significant difference (P< 0.05) between NAA and AA, after adjusting for age, gender, BMI and smoking, †) significant difference (P< 0.05) between NAA and controls, ‡) significant difference (P< 0.05) between AA and controls
**Risk factors during childhood:**

Known childhood risk factors for asthma like a severe lung disease or a respiratory infection at young age did not differ in frequency between the two asthma groups and neither did heredity for asthma (Figure 6, table 6). But parental allergy was significantly more common in the allergic asthma compared to the non-allergic asthma group. When adjusting for age, gender, BMI and smoking it showed that being hospitalized before the age of 2 years for lung disease, having a severe respiratory infection before the age of 5 years, parental allergy and parental asthma were all independent risk factors for both non-allergic and allergic asthma. The relative risk of asthma when having an allergic parent was significantly greater for those with allergic asthma compared to those with non-allergic asthma (Table 7).

To have had a shared bedroom under the age of 5 years was more common in the non-allergic asthma group compared to the allergic asthma and control groups. Living with either cat or dog before the age of 1 was also more common in the non-allergic asthma group compared to the allergic asthma and control groups. But these differences were no longer significant after adjusting for age, gender, BMI and smoking (Figure 6, table 6).

Living on a farm during childhood was significantly more common in the non-allergic asthma group compared to the allergic asthma and control groups. A multiple regression analysis showed that living on a farm during childhood and attending daycare before the age of 5 were both independent risk factors for non-allergic asthma, but not for allergic asthma (Table 7).

Parental smoking was common, but no differences between any of the groups were found.
Figure 4, Prevalence of risk factors during childhood for allergic asthma, non-allergic asthma and controls (%)

*Significant difference (P< 0.05) between NAA and AA, after adjusting for age, gender, BMI and smoking, †) significant difference(P< 0.05) between NAA and controls, ‡) significant difference (P< 0.05) between AA and controls

Table 6, Prevalence of risk factors during childhood for allergic asthma, non-allergic asthma and controls (%)

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Control (n219)</th>
<th>Non-allergic asthma (n174)</th>
<th>P-value*</th>
<th>Allergic asthma (n401)</th>
<th>P-value†</th>
<th>P-value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalized &lt;2y for lung disease</td>
<td>1.4</td>
<td>8.1</td>
<td>0.001</td>
<td>8.2</td>
<td>&lt;0.001</td>
<td>0.95</td>
</tr>
<tr>
<td>Severe resp. infection &lt;5y</td>
<td>6.67</td>
<td>23.1</td>
<td>&lt;0.001</td>
<td>21.5</td>
<td>&lt;0.001</td>
<td>0.70</td>
</tr>
<tr>
<td>Parent ever asthma</td>
<td>11.0</td>
<td>37.9</td>
<td>&lt;0.001</td>
<td>32.7</td>
<td>&lt;0.001</td>
<td>0.22</td>
</tr>
<tr>
<td>Parent ever allergy</td>
<td>32.9</td>
<td>41.0</td>
<td>0.10</td>
<td>57.9</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Shared bedroom &lt;5y</td>
<td>33.5</td>
<td>44.7</td>
<td>0.025</td>
<td>33.8</td>
<td>0.93</td>
<td>0.014</td>
</tr>
<tr>
<td>Daycare &lt;5y</td>
<td>25.6</td>
<td>31.9</td>
<td>0.17</td>
<td>35.8</td>
<td>0.01</td>
<td>0.38</td>
</tr>
<tr>
<td>House pet &lt;1y</td>
<td>27.8</td>
<td>38.3</td>
<td>0.03</td>
<td>30.4</td>
<td>0.51</td>
<td>0.06</td>
</tr>
<tr>
<td>Living on a farm</td>
<td>7.3</td>
<td>16.1</td>
<td>0.006</td>
<td>6.2</td>
<td>0.60</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Parental smoking</td>
<td>66.5</td>
<td>66.5</td>
<td>1</td>
<td>61.3</td>
<td>0.20</td>
<td>0.24</td>
</tr>
</tbody>
</table>

*P-value* = between control/NAA, †P-value* = between control/AA, ‡P-value* = between NAA/AA
Table 7, Adjusted odds ratio (OR) for risk factors during childhood (95% CI).

**Adjusted for age, gender, BMI and smoking.**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Non-allergic asthma</th>
<th>Allergic asthma</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalized &lt;2y</td>
<td>7.62 (2.10-27.6)</td>
<td>6.51 (1.94-21.8)</td>
<td>0.65</td>
</tr>
<tr>
<td>Severe respiratory infection &lt;5y</td>
<td>3.78 (1.91-7.50)</td>
<td>3.94 (2.11-7.35)</td>
<td>0.87</td>
</tr>
<tr>
<td>Parent asthma</td>
<td>3.01 (2.01-4.51)</td>
<td>2.50 (1.73-3.60)</td>
<td>0.29</td>
</tr>
<tr>
<td>Parent allergy</td>
<td>1.89 (1.36-2.63)</td>
<td>1.89 (1.42-2.52)</td>
<td>0.01</td>
</tr>
<tr>
<td>Daycare &lt;5y</td>
<td>1.71 (1.04-2.81)</td>
<td>1.19 (0.79-1.79)</td>
<td>0.10</td>
</tr>
<tr>
<td>House pet &lt;1y</td>
<td>1.50 (0.97-2.34)</td>
<td>1.11 (0.76-1.63)</td>
<td>0.13</td>
</tr>
<tr>
<td>Shared bedroom &lt;5y</td>
<td>1.49 (0.97-2.30)</td>
<td>1.18 (0.81-1.70)</td>
<td>0.39</td>
</tr>
<tr>
<td>Living on a farm</td>
<td>2.29 (1.16-4.53)</td>
<td>0.98 (0.50-1.93)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

*P-value = between NAA and AA*

**Environmental factors:**

No significant differences were found between any of the groups for the environmental factors. However, the relative risk of having allergic asthma was significantly increased if the subject had been living in a house with dampness in the floor construction after adjusting for age, gender, BMI, smoking and educational level (Table 9). Ever having worked in an environment with exposure for gas, dust or smoke was more common in the two asthma groups compared to the control group, but there was no significant difference between the two asthma groups (Figure 7, table 8). After adjusting, the relative risk of having non-allergic asthma was significantly associated with ever having worked in an environment with exposure for gas, dust or smoke. Exposure to high levels of gas, dust or smoke at a single incident was significantly more common in the non-allergic asthma group compared to the allergic asthma and control group. The relative risk of asthma connected to high exposure at a single incident was significantly increased for non-allergic asthma only. The non-allergic asthma group had more often finished school at 16 years of age or younger compared to the allergic asthma group.

Table 8, Impact of exposure to dampness, mould, gas, dust, smoke and subjects educational level (%).

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Control (n219)</th>
<th>Non-allergic asthma (n174)</th>
<th>P-value&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Allergic asthma (n401)</th>
<th>P-value&lt;sup&gt;2&lt;/sup&gt;</th>
<th>P-value&lt;sup&gt;3&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Damage in home by water leak-dampness &lt;12m</td>
<td>7.8</td>
<td>5.2</td>
<td>0.30</td>
<td>8.2</td>
<td>0.89</td>
<td>0.21</td>
</tr>
<tr>
<td>Dampness in floor construction &lt;12m</td>
<td>1.4</td>
<td>5.4</td>
<td>0.03</td>
<td>7.7</td>
<td>0.001</td>
<td>0.33</td>
</tr>
</tbody>
</table>
Co morbidity:

Having been diagnosed with chronic obstructive pulmonary disease (COPD) was more common in the non-allergic asthma group compared to the allergic asthma and control groups (Figure 8, table 10). Currently taking medication for high blood pressure was also more common in the non-allergic asthma group compared to the allergic asthma group, as was having diabetes. No significant differences regarding co-morbidity remained after adjusting for age, gender, BMI and smoking history.
**Figure 5, Co morbidity; chronic obstructive pulmonary disease (COPD), high blood pressure (BP) or diabetes for allergic asthma, non-allergic asthma and controls (%)**

![Co morbidity (%) graph]

*Significant difference between NAA and AA, after adjusting for age, gender, BMI and smoking, †) significant difference between NAA and controls, ‡) significant difference between AA and controls

**Table 10, Co morbidity; chronic obstructive pulmonary disease (COPD), high blood pressure (BP) or diabetes for allergic asthma, non-allergic asthma and controls (%)**

<table>
<thead>
<tr>
<th></th>
<th>Control (n219)</th>
<th>Non-allergic asthma (n174)</th>
<th>P-value*</th>
<th>Allergic asthma (n401)</th>
<th>P-value†</th>
<th>P-value‡</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ever diagnosed COPD</td>
<td>0.9</td>
<td>13.3</td>
<td>&lt;0.001</td>
<td>3.5</td>
<td>0.052</td>
<td>&lt;0.001</td>
<td>0.06</td>
</tr>
<tr>
<td>Medicating for high BP</td>
<td>13.0</td>
<td>22.6</td>
<td>0.02</td>
<td>8.5</td>
<td>0.08</td>
<td>&lt;0.001</td>
<td>0.22</td>
</tr>
<tr>
<td>Medicating for diabetes</td>
<td>3.4</td>
<td>6.8</td>
<td>0.14</td>
<td>1.9</td>
<td>0.25</td>
<td>0.004</td>
<td>0.17</td>
</tr>
</tbody>
</table>

*P-value* = between control/NAA, *P-value* = between control/AA, *P-value* = between NAA/AA, *P* = P-value between NAA/AA, adjusted for age, gender, BMI and smoking

**Quality of life:**

The Mini Asthma Quality of Life Questionnaire (mAQLQ) overall score and the scores of each of the four domains were significantly lower in the non-allergic asthma group compared to the allergic asthma group (Figure 9, Table 11). The significant difference in overall score of mAQLQ remains after adjusting for age, gender, BMI and smoking.
Figure 6, Scores from the Mini Asthma Quality of Life Questionnaire (mAQLQ)

Results of mAQLQ

*Significant difference (P< 0.05) between NAA and AA, after adjusting for age, gender, BMI and smoking

Table 11, Scores from the Mini Asthma Quality of Life Questionnaire (mAQLQ) (SD)

<table>
<thead>
<tr>
<th></th>
<th>Non-allergic asthma</th>
<th>Allergic asthma</th>
<th>P-value</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>mAQLQ (overall)</td>
<td>5.5 ± 1.1</td>
<td>6.0 ± 0.9</td>
<td>&lt;0.001</td>
<td>0.011</td>
</tr>
<tr>
<td>- Symptoms</td>
<td>5.4 ± 1.2</td>
<td>5.8 ± 0.06</td>
<td>&lt;0.001</td>
<td>0.013</td>
</tr>
<tr>
<td>- Activities</td>
<td>5.8 ± 1.3</td>
<td>6.2 ± 1.1</td>
<td>0.001</td>
<td>0.037</td>
</tr>
<tr>
<td>- Emotions</td>
<td>5.7 ± 1.2</td>
<td>6.1 ± 1.1</td>
<td>0.002</td>
<td>0.073</td>
</tr>
<tr>
<td>- Environmental</td>
<td>5.5 ± 1.3</td>
<td>6.0 ± 1.2</td>
<td>&lt;0.001</td>
<td>0.027</td>
</tr>
</tbody>
</table>

P-value = between NAA and AA, P* = P-value between NAA/AA, adjusted for age, gender, BMI and smoking
Discussion

In this Swedish multicenter cohort of the GA²LEN follow-up study, we found significant differences between the allergic and non-allergic forms of asthma regarding clinical expressions. We found significantly more cough and phlegm production in non-allergic asthma and more wheezing in allergic asthma. As expected the allergic asthma group had a significantly higher frequency of other atopic diseases, but more unexpectedly we found that the non-allergic asthma group also had other atopic diseases, such as eczema and rhinitis, significantly more often than the control group. We also found that early life events, such as severe respiratory infections that lead to hospitalization, plays a significant role in both development of allergic and non-allergic asthma, even though the non-allergic asthma has a much higher mean age of debut. The group with non-allergic asthma scored significantly lower on the quality of life questions compared to both those with allergic asthma and controls.

In our cohort, non-allergic asthma had a prevalence of 30%, which is in the same range as what has been reported before [5, 31]. The group of allergic asthma was significantly younger than the non-allergic asthma group in our study population. The non-allergic asthma group had the highest amount of women, but the difference was only statistically significant compared to controls. In the allergic asthma and control groups it was close to equal distribution between men and women. These findings are in accordance with previous studies [5, 31]. Leynaert et al. suggest that the overrepresentation of women in the non-allergic form of asthma are likely to be due to some biological factors that significantly differ between men and women, which matter in the development of non-allergic asthma [24].

The higher mean values of BMI in individuals with asthma compared to healthy controls have also been shown numerous times before [26, 33, 38]. In our study, the non-allergic asthma group also had significantly higher mean value of BMI than the allergic asthma group. In line with this, Appleton et al. found in a large population based study that central obesity (waist circumference and waist-hip-ratio) was significantly associated with increased risk for non-allergic asthma, but not for allergic asthma [34]. Smoking was significantly more common in the non-allergic asthma group, which is consistent with earlier findings [5, 29, 31]. It is only possible to speculate on whether smoking causes non-allergic asthma or if in fact those with allergic asthma have a lower rate of ever smoking because of their lower mean age of asthma diagnosis and therefore being less likely to start smoking due to having asthma. However, when the relative risk of asthma and smoking was calculated there was no statistical significance for either group, which is in contrast with the results of for example Ulrik et al. who found that current and previous smoking is an important risk factor for non-allergic asthma [29].
A significant difference in lung function, with lower FEV1 in the non-allergic asthma group compared to the allergic asthma group, was found. But this difference was mainly due to the differences in age, gender, BMI and smoking between the asthma groups and was no longer statistically significant after adjusting for these factors. The ENFUMOSA study on severe asthma showed that those with a severe form of asthma, and therefore lower FEV1, were more often skin prick negative, or in other words non-allergic asthmatics [18]. Previous studies has also found that those with non-allergic asthma has a lower FEV1 compared to those with allergic asthma, but in these studies the values have not been adjusted for differences between the groups (age, gender, BMI, smoking) [5, 31]. In another study by Little et al. it is shown that high sputum neutrophils (a marker for non-allergic severe asthma) and long duration of disease are independently associated with low FEV1, even after adjusting for age [19]. We found that a significantly larger proportion of those with non-allergic asthma had a FEV1/VC ratio below 0.70 compared to those with allergic asthma, which shows that those with non-allergic asthma more often have a persistent airflow obstruction. There is a fine line between having asthma with persistent airflow obstruction and having COPD. Far from all asthma patients show full reversibility on airflow obstruction, and not all COPD patients have low reversibility on airflow obstruction, with bronchodilator tests. In a review by Pascual et al. on persistent airflow obstruction in patients with asthma, it is concluded that there is sufficient evidence to state that there is a subgroup of asthma patients that develop an irreversible airflow obstruction, and it is strongly suggested that this most often occur for those with severe asthma [53]. For these patients the difference between asthma and COPD becomes even smaller.

As predicted the inflammatory markers IgE and FeNO had a strong association with allergic asthma in the current study, which has been found in several studies before [5, 12]. It is clinically important to distinguish between these two forms of asthma and these findings are therefore useful since it is easy and not very costly to test the asthma patient for serum IgE, FeNO and a skin pick test.

Previous studies have found that those with non-allergic asthma often have a more severe expression of asthma [5]. In our study we found that the distribution of symptoms differed between the two asthma groups. The most prominent symptom for the non-allergic asthmatics was chough and production of phlegm. Wheezing, which is a more classical asthma symptom, was more common in the allergic asthma group. These findings are consistent with the results of Knudsen et al. who found the same distribution of symptoms [31].

We found no difference in the prevalence of CRS between the asthma groups, but the prevalence was significantly increased compared to the control group. We did, however, find that the allergic asthma group had a higher prevalence of allergic rhinitis, rhinitis, eczema,
rashes and food hypersensitivity, compared to the non-allergic and the control groups. We also found that those with non-allergic asthma reported these atopic diseases significantly more often compared to healthy controls. To our knowledge no prior study has been able to show this connection between non-allergic asthma and eczema, rashes and food hypersensitivity. A study on asthma and rhinitis suggests that rhinitis (upper airway disease) and asthma (lower airway disease) might in fact be connected as one common disease and that there is likely a systemic inflammatory component in asthma [54]. Our results also suggest that there could be a systemic component in asthma, for both the allergic and the non-allergic form, involving the immune system.

Regarding risk factors we found that being hospitalized before 2 years of age for lung disease or having a severe respiratory infection before age of 5 years were independent risk factors to later in life develop both allergic and non-allergic asthma. This indicates that both kinds of asthma are in fact somewhat induced by events in early life, even though non-allergic asthma has a higher mean age of debut. Janson et al. found in a study of risk factors for asthma among adolescents that non-allergic asthma was associated with certain early life events such as croup and frequent otitis [26]. Being raised on a farm was significantly more common for those with non-allergic asthma compared to both those with allergic asthma and controls, and when calculating the relative risk it also was an independent risk factor for non-allergic asthma. Unfortunately we do not have the data on to what extent these individuals grew up to be farmers themselves. Being a farmer is an occupation with known risk for developing asthma [55]. Alternatively childhood exposure alone could be a risk factor for non-allergic asthma. Lampi et al. found in a study that being born to a family with farm animals reduced the risk of having a doctors diagnosis of asthma and other atopic diseases at the age of 31 [56], which could imply that living on a farm reduces the risk of atopy and allergic asthma. A much debated issue is that of the risk, or protection, of having a house pet (eg. dog or cat) during childhood [44]. In our study we found no significant relative risk of asthma for participants who lived with either cat or dog before the age of 1 year, even though it was significantly more common for those with non-allergic asthma compared to both allergic asthma and controls.

We also found some important environmental risk factors, including that working in environments with elevated levels of either gas or dust or smoke were independent risk factors for developing both allergic and non-allergic asthma. Having being exposed of very high or extremely high levels of gas or dust or smoke was an independent risk factor for non-allergic asthma alone. This implies that both allergic and non-allergic asthma could be induced both by events in early life, as discussed above, but also by incidents and long term exposure as an adult.
Heredity has been found to play an important role in both asthma types, but especially for allergic asthma [26]. We found in our study that both parental allergy and parental asthma was independent risk factors for both non-allergic and allergic asthma, with no significant differences between the groups.

The non-allergic asthma group had a significantly lower overall score on the mini asthma quality of life questionnaire (mAQLQ) and also in all the underlying domains, except in the domain of emotions. This is in accordance with a study of Ehrs et al. who found that quality of life was ranked higher of those with allergic asthma compared to those with non-allergic asthma [57]. The mAQLQ has good measurement properties even though they are not quite as strong as those of the original Asthma Quality of Life Questionnaire, but AQLQ is not suitable for a study of this size [52]. In a recent study by Ek et al. it is shown that asthma-related quality of life is partially due to several modifiable factors such as smoking and obesity. This should therefore be considered by the physician when discussing quality of life with the asthmatic patient [46].

One of the strengths of this study is that the cohort is both large and based on a randomly selected group from the general population, which means that findings are applicable to any similar population. A major issue of previous studies has been that only those with severe asthma have been included [24, 31]. This problem is not present in the current study because of the cohort being based on the general population. This large multicenter study also has a great strength in the cohorts big age rage, 17-76 years. There is a lack of knowledge in this area since many studies exclude elderly patients. Other studies show that elderly patients may underestimate symptom severity and attribute breathlessness to age and other comorbidities [58]. However, a weakness in the present study is the possible misclassification of individuals with early symptoms of COPD, whom theoretically could have been included in the non-allergic asthma group. Almost one third of those with non-allergic asthma had a FEV1/VC ratio below 0.70, which is the spirometric definition of COPD [59]. In our study asthma diagnosis was self-reported, together with either self-reported asthma symptoms or asthma treatment during the last year. It could be that some of those included in the non-allergic asthma group had both COPD and asthma, or only COPD and no asthma. 13.3% of those included in the non-allergic asthma group have reported to also have a COPD diagnosis. The selection of the groups for this study is based on a questionnaire and hence has the self-reported diagnosis played a significant role in the results. No additional reading of medical journals for verification of diagnoses have been done, which is a weakness in the results.

**Conclusion:**
In conclusion, the most important findings in this study is that non-allergic and allergic asthma differs in many important ways. The distribution of symptoms differs in that non-
allergic asthma has more cough and phlegm while those with allergic asthma suffer more from wheezing. We have also seen the impact of early life events affecting the airways and also certain environmental risk factors, particularly for the risk of developing non-allergic asthma. We have also further established the view of non-allergic asthma as an often more severe form of asthma shown in the lower ratings of the asthma related quality of life, with a later debut in life and a female dominance.
Reference list

12. Ehrs, Quality of life and inflammatory markers in mild asthma. 2006.
27. Rönmark, *Different pattern of risk factors for atopic and nonatopic asthma among children-report from the Obstructive Lung Disease in Northern Sweden Study*. 2001
46. Ek, A., *CRS in asthma is a negative predictor of quality of life* Allergy, 2013. In press.


Appendix
Postal questionnaire from the GA\textsuperscript{2}LEN Survey

TO ANSWER THE QUESTIONS PLEASE TICK THE APPROPRIATE BOX

IF YOU ARE UNSURE OF THE ANSWER PLEASE CHOOSE ‘NO’

1. Have you had wheezing or whistling in your chest at any time \textit{in the last 12 months}?

\textbf{IF ‘NO’ GO TO QUESTION 2} \hspace{1cm} \textbf{IF ‘YES’ GO TO QUESTION 1.1}

1.1 Have you been at all breathless when the wheezing noise was present?

1.2 Have you had this wheezing or whistling when you did \textit{not} have a cold?

2. Have you woken up with a feeling of tightness in your chest at any time \textit{in the last 12 months}?

3. Have you been woken by an attack of shortness of breath at any time \textit{in the last 12 months}?

4. Have you been woken by an attack of coughing at any time \textit{in the last 12 months}?
5. Do you bring up phlegm from your chest on most days for as much as three months each year?

   NO  YES

6. Have you ever had asthma?

   IF ‘NO’ GO TO QUESTION 7

6.1 How old were you when you had your first attack of asthma?

   YEARS

   (If unsure, give your best guess!)

6.2 Have you ever been hospitalised with asthma?

6.3 Have you had an attack of asthma in the last 12 months?

6.4 Are you currently taking any medicine (including inhalers, aerosols or tablets) for asthma?

7. Do you have any nasal allergies including hay fever?

   IF ‘NO’ GO TO QUESTION 8

   IF ‘YES’ GO TO QUESTION 7.1
7.1 Have you been troubled by nasal allergies in the last 12 months?  

7.2 Have you ever been troubled by nasal allergies for more than 4 days in any one week?  

7.3 If yes did this happen for more than 4 weeks continuously?  

8. Has your nose been blocked for more than 12 weeks during the last 12 months?  

9. Have you had pain or pressure around the forehead, nose or eyes for more than 12 weeks during the last 12 months?  

10. Have you had discoloured nasal discharge (snot) or discoloured mucus in the throat for more than 12 weeks during the last 12 months?  

11. Has your sense of smell been reduced or absent for more than 12 weeks during the last 12 months?  

12. Has a doctor ever told you that you have chronic sinusitis?  

13. Have you ever had an itchy rash that was coming and going for at least 6 months?  

IF NO, GO TO QUESTION 14  
IF ‘YES’ GO TO QUESTION 13.1
13.1 Have you had this itchy rash in the last 12 months?

13.2 Does this affect only your hands?

14. Have you ever had eczema or any kind of skin allergy?

15. Have you ever had any difficulty with your breathing within 3 hours after taking a pain killer?

IF ‘NO’ GO TO QUESTION 16
IF ‘YES’ GO TO QUESTION 15.1

15.1 Please write the name of the tablet?

16. Have you ever smoked for as long as a year? 

[‘YES’ means at least one cigarette per day or one cigar per week for one year]

IF ‘NO’ GO TO QUESTION 17
IF ‘YES’ GO TO QUESTION 16.1

16.1 How old were you when you started smoking?

16.2 Have you smoked at all in the last month?
16.2.1 How old were you when you stopped smoking?

16.3 On average how much do you (or did you) smoke?

Tick one box only!

17. Are you currently:
   a. employed
   b. self-employed
   c. unemployed
   d. not working because of poor health
   e. full-time house person
   f. full-time student
   g. retired
   h. other

18. Are you currently working:
   a. As a health care worker (e.g. as a nurse, medical technician, doctor, paramedic or similar)?
   b. In a job that is mainly involved with any sort of cleaning?

19. How tall are you?
20. What is your current weight?

21. What is your date of birth?

22. What is today’s date?

23. Are you male or female?

23. What is your postcode/zip code?

May we contact you again to help us further with this research and to provide further information?

Thank you for your help!