Symptomatic and asymptomatic airway hyperresponsiveness
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Chapter 1

GENERAL INTRODUCTION
Background

For many years, an intensive collaboration exists between different disciplines at the University and University Hospital of Groningen (the Netherlands) performing research on asthma and chronic obstructive lung disease (COPD): the CARA Research Group Groningen. The project described in this thesis originated from this interdisciplinary research group in which, for this project, the departments of Epidemiology and Statistics, Pathology, and Pulmonary Diseases participated.

Most individuals who experience respiratory symptoms, such as chronic cough and phlegm, bronchitic episodes, persistent wheeze, dyspnea, and asthma attacks, also have airway hyperresponsiveness (AHR) (1-3). Results of the 25 year longitudinal population study in Vlagtwedde and Vlaardingen in the Netherlands showed that despite the strong relationship between the presence of respiratory symptoms and AHR, they are not inseparable (1). The majority of the population experiences no respiratory symptoms and no AHR (56.5%), whereas 10.2% experiences both respiratory symptoms and AHR. In addition, 14.3% of the population has no respiratory symptoms but does have AHR, and another 19.0% does have respiratory symptoms without AHR. In the current thesis, we have investigated factors that are independently associated with either the solitary or simultaneous presence of respiratory symptoms and airway hyperresponsiveness. These analyses concern data collected during the 25 year follow-up of the Vlagtwedde-Vlaardingen Study (1965-1990).

An important underlying mechanism of respiratory symptoms and AHR in individuals with asthma or COPD is an inflammatory process in the airways (4). Therefore, we also investigated whether an inflammatory process exists in the airways of individuals with respiratory symptoms yet without AHR and, conversely, in individuals without respiratory symptoms and with AHR. To this aim we collected new data on a sample of subjects who participated in one of the final surveys at Vlagtwedde in 1985 or 1989.

The Vlagtwedde-Vlaardingen Study (1965-1990)

In 1965, an extensive longitudinal population study was started to obtain information on the prevalence of chronic nonspecific lung disease (CNSLD), a disease entity encompassing both asthma and COPD. Moreover, the etiology of CNSLD, the natural course, and the significance of early symptoms in the development of this condition was investigated (5). Air pollution and smoking were considered important etiologic factors. To investigate the effects of air pollution on the development of CNSLD, the study was performed in two different areas in the Netherlands: the rural area of Vlagtwedde, in the north-east of the Netherlands, and the urban, industrial area of Vlaardingen, in the south-west of the country. The first surveys consisted of a random sample of both areas of all men and women aged 40 to 64 years in 1965, and a random sample of all men and women aged 15 to 39 years in 1967 at Vlagtwedde and in 1969 at Vlaardingen. The cohorts for the longitudinal study consisted of the youngest men and women who participated in 1965 (40 to 44 years at Vlagtwedde and 40 to 54 years at Vlaardingen), and all participants in 1967 and 1969 (aged 15 to 39 years). After the baseline surveys the cohorts participated in follow-up surveys approximately every 3 years (Table 1). The final surveys were organized in 1989 at Vlagtwedde and in 1990 at Vlaardingen. At Vlagtwedde the number of participants slightly increased during the follow-up, because at each follow-up survey all men and women born between 1921 and 1952 and living in a circumscribed area in Vlagtwedde were invited independent whether they
participated before. All surveys were carried out during the month of October.

### Table 1. Surveys of the longitudinal Vlagtwedde-Vlaardingen Study

<table>
<thead>
<tr>
<th>Cohort</th>
<th>baseline surveys</th>
<th>follow-up surveys</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N= 450* 1,793)</td>
<td>2,109 2,245 2,212 1,910 1,973 1,819 1,753)</td>
</tr>
<tr>
<td></td>
<td>(N= 859* 1,590)</td>
<td>1,679 1,384 1,219 1,214 977 884 800)</td>
</tr>
</tbody>
</table>

* only the youngest (40 to 44 yr at Vlagtwedde and 40 to 54 yr at Vlaardingen) who were invited to participate in the cohort.

In total, 5247 individuals participated in the longitudinal population study at Vlagtwedde and 2790 individuals at Vlaardingen.

The study has several aspects that are unique in studies on asthma and COPD at that time. Examples are the measurements of airway responsiveness and peripheral blood eosinophils in each survey from 1965 onwards, and of skin test positivity in the baseline surveys and the first follow-up surveys. Airway responsiveness to histamine was assessed in a 25% random sample of the study population. At the first study only, a small random selection of 38 individuals (older than 40 yr) with prevalent respiratory symptoms was added for assessment of airway responsiveness. From the third survey onwards, airway responsiveness was tested in those subjects who had undergone a test of airway responsiveness in prior surveys as well. If time permitted, an additional random sample of subjects from the cohort was added for assessment of airway responsiveness.

### Airway hyperresponsiveness

A characteristic feature of asthma and COPD is airway hyperresponsiveness (6). Airway hyperresponsiveness is the exaggerated airway narrowing due to non-specific stimuli, such as cold, fog, baking fumes and perfume, and to pharmacological stimuli, such as histamine and methacholine. The underlying mechanisms of airway hyperresponsiveness may vary with different types of respiratory symptoms and with differences in severity. This is also suggested by the different dose-response curves in subjects with asthma, rhinitis, and healthy subjects (7-9). In the Vlagtwedde-Vlaardingen Study, airway responsiveness was assessed by measuring the sensitivity of the airways after 30 seconds inhalation of doubling concentrations of histamine solutions. The sensitivity of the airways can be calculated from the dose-response curve as the concentration that causes a pre-determined decrease in the FEV₁ compared to baseline, e.g. 20% (PC₂₀ value). The Vlagtwedde-Vlaardingen Study used a 10% fall in FEV₁ from baseline (PC₁₀ value) to assess airway sensitivity to histamine.
Factors associated with airway hyperresponsiveness

Most individuals with AHR also experience respiratory symptoms, such as chronic cough and phlegm, bronchitis episodes, wheeze, and dyspnea, as is observed in individuals with asthma or COPD (1-3). A small proportion of them do not have respiratory symptoms, the so-called asymptomatic hyperresponsive subjects. Several studies have shown that asymptomatic subjects with AHR are at increased risk to develop respiratory symptoms compared to asymptomatic subjects without AHR (10-13). Genetic predisposition may play a role in the development of AHR (14,15). Environmental factors, such as smoking or allergen exposure, may interact with the genetic predisposition in the development of respiratory symptoms. Population studies have shown associations between AHR and various risk factors, including cigarette smoking (16-21), skin test positivity (17,22), increased serum total IgE level (23,24), peripheral blood eosinophilia (25-27), older age (21,28), female gender (16,17,28,29,30), lower level of FEV₁ (16,17,21,31-34) and subsequent decline in FEV₁ (35-39). The association between an older age and AHR has been reported to be stronger in symptomatic subjects than in asymptomatic subjects (28). No further studies examined whether the association of the various risk factors with AHR is modified by the presence of respiratory symptoms. Thus, it is currently not known whether the other risk factors are specifically associated with symptomatic AHR or also with asymptomatic AHR.

Mechanisms of airway hyperresponsiveness

The specific mechanisms by which AHR occur are unknown, although airway inflammation and structural changes of the airway wall (possibly caused by inflammatory changes) are considered to play an important role (40-47). Dysfunction of the autonomic nervous system of the smooth muscle may also contribute to AHR (42,44,46). Hypotheses about the dysfunction of the autonomic nervous system include a possible role of a dysfunction of the β-adrenergic (sympathetic) and cholinergic (parasympathetic) systems as well as the non-adrenergic non-cholinergic (NANC) system.

Structural changes of the airway wall

Structural changes may occur in the airway wall of individuals with asthma or COPD and contribute to the presence and severity of AHR. Such changes occur as an increased deposition of submucosal and adventitial tissue, increased mucous gland size as well as increased goblet cell number accompanied by excessive production of mucus, increased number of bronchial capillaries, and increased bronchial smooth muscle mass due to hypertrophy and hyperplasia (4,40,41,48,49). These structural changes may thicken the airway wall both in asthma and COPD, including the adventitial, submucosal, and smooth muscle layer. Airway wall thickening can narrow the airways and exacerbate airway responsiveness (48). Epithelial damage may also contribute to increased airway responsiveness. Loss of mucus clearance contributes to airway obstruction by formation of mucus plugs. Further, epithelial damage results in increased exposure of the afferent nerves to irritants and inflammatory mediators, resulting in reflex bronchoconstriction. Epithelial damage also inhibits the release of a relaxing factor by epithelial cells.
**Airway inflammation**

Inflammation of the airways plays an important role in the pathogenesis of bronchial hyperresponsiveness in asthma and COPD, involving various cells and their mediators, vascular adhesion molecules, and extra-cellular matrix components (4,49). These are, however, of different nature in asthma and COPD. Airway inflammation can be assessed by different methods including measurement of NO in exhaled air, and of inflammatory cells and mediators in induced sputum, bronchoalveolar lavage, and airway wall and transbronchial biopsies, providing information on different compartments of the airways (50,51). Important aspects of airway inflammation are changes in the number as well as in the activation state of inflammatory cells. The type, severity, and location of inflammation is different between asthma and COPD (4,49,52). Allergy is present in most asthmatics. The inflammatory process in the airways of asthmatics is characterized by an increase in number and in activation state of T-lymphocytes, predominantly CD4+ cells, increased number of eosinophils with a higher percentage of degranulated eosinophils, and shedding and activation of epithelial cells (4,53-55). Smoking is a major causative factor of airway inflammation in COPD. The inflammatory process in the airways of COPD patients is characterized by an increase in number and activation state of T-lymphocytes, predominantly CD8+ cells, increased number of eosinophils, although to a far lesser extent than in asthma and more explicitly so during exacerbations, increase in number and activation state of macrophages, increased number of neutrophils, and metaplasia of the epithelium (4,55-62).

Pharmacologic studies support the relationship between airway inflammation and AHR (41). Treatment with anti-inflammatory drugs reduces both the increased airway responsiveness and the airway inflammation, whereas treatment with β2-agonists does not reduce airway inflammation and airway hyperresponsiveness, at least when the bronchodilating effect has waned off. However, regular use of glucocorticoids reduces asthma severity and the extent of airway inflammation, but rarely normalizes airway responsiveness. The results of these drug studies suggest that airway inflammation contributes to AHR but is not the only factor.

AHR is associated with airway remodelling and airway inflammation in asthma and COPD patients (4,48,63,64). AHR in asymptomatic subjects is associated with an increased risk to develop subsequent respiratory symptoms (10-13). Therefore, the question raises whether airway remodelling and inflammation in the airways contribute to the presence of AHR in asymptomatic individuals.

**Aims of the thesis**

The main goal of the current thesis is to determine the factors associated with the single or simultaneous presence of respiratory symptoms and airway hyperresponsiveness. Therefore, we investigated the risk factors associated with the presence of respiratory symptoms and airway hyperresponsiveness (cross-sectionally and longitudinally in a retrospective way), and with the development of respiratory symptoms in individuals with and without airway hyperresponsiveness (longitudinally in a prospective way). Further, we investigated whether inflammatory changes in the airways may play a role in the presence of either respiratory symptoms, or AHR, or their combination.
Chapter 1

The specific questions addressed in this thesis are:

1. Which associations with airway hyperresponsiveness have been described in the literature that may explain the presence of AHR in asymptomatic individuals, and which inflammatory processes are known in symptomatic subjects that may also play a role in AHR in asymptomatic subjects (Chapter 2)?

2. Are the atopy-related factors skin test positivity, increased serum total IgE levels, and peripheral blood eosinophilia related to AHR, and are the relationships the same in subjects with and without respiratory symptoms (Chapter 3)?

3. Do peripheral blood eosinophilia, skin test positivity, and cigarette smoking relate to the development of respiratory symptoms, and do they influence the increased risk to develop respiratory symptoms in individuals with hyperresponsiveness (Chapter 4)?

4. Do lung function growth and development differ between subjects with single or coinciding presence of respiratory symptoms and AHR at elderly age (Chapter 5)?

5. Do inflammatory processes exist in the airways of asymptomatic hyper-responsive subjects? If so, are these inflammatory processes quantitatively or qualitatively different from the inflammatory processes in the airways of symptomatic hyperresponsive subjects and are these related to the level of lung function (Chapters 6 and 6a)?

To answer these research questions we used already existing data from the Vlagtwedde-Vlaardingen Study from 1989 and 1990 (Chapter 3), and from 1965 to 1990 (Chapter 4 and 5). Further, we collected new data on a sample of subjects who participated in one of the final surveys at Vlagtwedde in 1985 or 1989 (Chapter 6 and 6a).

Chapter 7 concludes with a general discussion of the studies described in this thesis and future perspectives.
References


