# Airway sensory hyperreactivity linked to capsaicin sensitivity
# Definitions and epidemiology

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Hej sa My. Varför sitter du på taket?
Hej, hej, svarade Mini. Jag sover
utomhus i natt därför att jag är olfaktiv. …
Det betyder att jag är känslig för lukt.
Tove Jansson

Ur "Skurken i Muminhuset"
Bonniers Junior Förlag AB, 1980
(med tillstånd från förlaget)

To individuals with odour intolerance and
increased airway sensitivity
in the hope of better understanding
of this disease in the future.

# Airway sensory hyperreactivity linked to capsaicin sensitivity
## Definitions and epidemiology

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**Abstract**

**Aims:**

- To study the relationship between odour intolerance and capsaicin sensitivity and to develop a definition of airway sensory hyperreactivity (SHR).
- To study epidemiology of odour intolerance; particularly regarding airway symptoms, and to relate odour intolerance to possible risk factors.
- To investigate the relationships between SHR and other respiratory diseases.
- To study psychiatric morbidity at SHR.

**Material and methods:** Totally 2847 adult subjects were included in these studies; 55% of them were women and 897 were patients. Studies I and IV were performed among patients referred to the Allergy Centre at the Central Hospital of Skövde, Sweden. Study IV also included a group of asthma patients from three Care Centres. Study II was a cross-sectional, population-based epidemiological study of adult inhabitants in Skövde, and in study III randomly selected individuals from this population-based study were used. In all four studies, we used questionnaires to evaluate the symptoms arising from odour exposure, the consequences of these symptoms for the participants' social lives, and smoking habits. Olfactory function was evaluated in study II. Patients referred to the Allergy Centre were diagnosed with medical history, allergy investigations, and nose and pulmonary function tests when appropriate. In study IV methacholine tests were performed in patients with SHR in order to exclude asthma. Capsaicin inhalation tests were used in study I, III and IV.

**Results:** The limiting value for the capsaicin inhalation test was defined as 35 coughs after provocation with a concentration of either 0.4 or 2.0 µM capsaicin. The prevalence of SHR, defined as odour intolerance with affective and behavioural consequences and a positive capsaicin test, was estimated at 6% (95% CI: 4.2-8.4) in a general Swedish population. Odour intolerance with affective and behavioural consequences was reported by 19% (95% CI: 15-22), while one-third reported general odour intolerance. There was no evidence for an increased prevalence of SHR among asthma patients, an increased prevalence of asthma among SHR patients, any relationship between SHR and smoking, any relationship between SHR and depression or anxiety, nor any association between odour intolerance and changed sense of smell.

**Conclusions:** The diagnosis "Airway sensory hyperreactivity" (SHR) is proposed for patients with airway symptoms and affective reactions to and behavioural consequences of odour intolerance, who also have a positive capsaicin inhalation test.

**Keywords:** Capsaicin; chemical sensitivity; epidemiology; odour intolerance; sensory hyperreactivity;

# Table of contents

# List of original papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

I          Johansson A, Lowhagen O, Millqvist E, Bende M
Capsaicin inhalation test for identification of sensory hyperreactivity.
Respir Med. 2002 Sep;96(9):731-5.

II         Johansson A, Bramerson A, Millqvist E, Nordin S, Bende M.
Prevalence and risk factors for self-reported odour intolerance: the Skovde population-based study.
Int Arch Occup Environ Health. 2005 Aug;78(7):559-64.

III       Johansson A, Millqvist E, Nordin S, Bende M
Relationship between self-reported odour intolerance and sensitivity to inhaled capsaicin: proposed definition of airway sensory hyperreactivity and estimation of its prevalence.
Chest. 2006 Jun;129(6):1623-8.

IV       Johansson Å, Millqvist E, Bende M
Relationship between airway sensory hyperreactivity and asthma.
In manuscript. 2008.

# Definitions

### Chemical sensitivity

Self-reported problems related to exposure to non-toxic concentrations of chemicals. The definition includes circumstances related to non-odourous exposure. See Odour intolerance.

### Odour sensitivity

Self-reported problems related to exposure to odours and pungents. The term "Odour sensitivity" is often used as a synonym for Odour intolerance, but today it is sometimes preferred as a description of increased airway sensitivity to odours and pungents.

### Odour intolerance

Self-reported problems related to exposure to odours and pungents. In this thesis, the term is used as a synonym for Odour sensitivity. It is often used as a synonym for Chemical sensitivity, although this is really a wider concept.

### Odour intolerance with self-reported affective and behavioural consequences

Odour intolerance with self-reported affective reactions to odour exposure and behavioural disruptions in daily activities is defined as a score ≥43 on the Chemical Sensitivity Scale for Sensory Hyperreactivity (CSS-SHR).

### Sensory hyperreactivity (SHR)

This term was initially used for a group of patients with odour sensitivity and airway symptoms after simple clinical characteristics (I). In later studies, Airway Sensory Hyperreactivity (SHR) was defined as the combination of odour intolerance with affective reactions and behavioural disruptions in daily activities (measured by CSS-SHR score) and a pathological capsaicin inhalation test (III, IV).

# Abbreviations

| | |
|---|---|
| AAAAI | American Academy of Allergi, Asthma and Immunology |
| A$\delta$ | Nerve fiber type A$\delta$ |
| $\beta_2$ | beta-2 receptor |
| BMI | Body mass index |
| C2, C5 | Concentration causing two or five coughs, respectively, in response to a provocation |
| C-fiber | Nerve fibres of type C |
| CI | Confidence interval |
| CGRP | Calcitonin gene-related peptide |
| COPD | Chronic obstructive pulmonary disease |
| CSS | Chemical sensitivity scale |
| CSS-SHR | Chemical sensitivity scale for sensory hyperreactivity |
| GINA | Global Initiative for Asthma |
| EEG | Electroencephalogram |
| ERP | Event-related potential in EEG after stimulation |
| $FEV_1$ | Forced expiratory volume in one second after a maximal inspiration |
| HAD | Hospital anxiety and depression scale |
| IEI | Idiopathic environmental intolerance |
| NGF | Nerve growth factor |
| MCS | Multiple chemical sensitivity |
| OR | Odds ratio |
| $PC_{20}$ | Concentration causing a 20% fall compared to pre-provocation value |
| PET scan | Positron emission tomography imaging |
| SHR | Airway sensory hyperreactivity |
| SP | Substance P |
| SOIT | Scandinavian Odour-Identification Test |
| TRP | Transient receptor potential channel |
| TRPV-1 | Transient receptor potential channel – vanilloid receptor 1 |
| VR-1 | Vanilloid receptor 1 |
| WHO | World Health Organization |

# Introduction

In their daily clinical work, physicians analyze symptoms, define diseases, and try to find causes. One significant challenge in this endeavour is patients with symptoms which after close examination still do not fit into any generally accepted diagnoses; this is even more troublesome for the patients who feel that their symptoms are misunderstood. This thesis deals with one such group of patients.

Airway reactions to chemicals and odours are essential protective biological mechanisms against inhalation of toxic substances. However, in a certain group of individuals, airway symptoms and sometimes general symptoms are induced by exposure to concentrations of odours and irritating chemical substances such as perfumes, flower scents, and car exhausts, which are normally regarded as non-toxic. These individuals have been described as having intolerance to odours and pungent substances, but still do not fit into any generally accepted diagnosis, despite careful examinations for obstructive pulmonary disease, allergy, other immunological disturbancies, or cardiovascular, gastrointestinal, or neurological diseases.

## Historical background

Patients with a history of chemical intolerance have been studied throughout the world, and a number of attempts have been made to define and explain the complexity of their symptoms. Failure of human adaption to changes in society and environment have been hypothesized to cause disease since the industrial revolution, and exposure to new chemicals and pungents even in low concentrations has often been in focus. Opinions about etiology and pathogenesis have changed from time to time. Exposure to toxic levels of chemicals can be harmful, and can cause structural damage and inflammation in the airways (1); and the capability of airborne chemicals to produce sensory irritation and protective reflex reactions has been carefully studied (2). Nearly a hundred years ago, it was found that animals pre-treated with strychnine reacted more strongly to sensory stimulation in upper airways than did control animals (3). However, questions have been raised over the evidence that prolonged increased airway sensitivity can be caused by exposure to levels of airborne chemicals which are normally regarded as non-toxic.

Multiple chemical sensitivity (MCS) is one example of a proposed diagnosis; it is characterized by symptoms from various organs as a response to exposure to low concentrations of chemicals in the environment (4). The symptoms are similar to those described for sick building syndrome (5). There have been great difficulties in finding

measurable physiological parameters linked to these syndromes, and shortly after the publication of Cullen's work, MCS was described by some researchers as a mental disorder (6). However, many patients with MCS show no sign of psychiatric morbidity, and no psychiatric theory or treatment has been established (7). An investigation of young adults reported a high prevalence of odour intolerance, but in contrast to expectations found no association with anxiety or depression (8). Other researchers have emphasized the interactions between the olfactory and trigeminal systems, and the possibility of learned behaviours or other cognitive or emotional reactions as a result of odour exposure, as possible mechanisms underlying the symptoms (9-11).

Exposure and reactions to chemicals have attracted attention from the perspective of workers' health, but the lack of scientific evidence for MCS as a toxicologically mediated disorder has made the use of this terminology a matter of doubt and discussion. Idiopathic environmental intolerance (IEI), once proposed as a diagnosis by Randolph in 1950, has been recommended instead of MCS because it does not point out the exposure as the cause of the problems. Summaries of this subject field are given in ´Workshop on MCS´ (12) and in ´Position statement of the AAAAI board of directors´ (13). As is the case for MCS, the symptoms of IEI are often regarded as reflecting psychological problems; e.g. after applying Bradford Hill's criteria (14-16).

Other research groups have proposed diagnoses for individuals with airway symptoms which cannot be explained by generally accepted diseases. Löwhagen described an "asthma-like" functional respiratory disorder related to odour and pungent exposure (17). Individuals with these symptoms often have symptoms from both upper and lower airways, and sometimes also general symptoms, so the condition was later renamed functional breathing disorder (18).

Another syndrome which was proposed to define these problems was hyperventilation syndrome, which is characterized by a variety of somatic symptoms, induced by physiologically inappropriate hyperventilation, and reproduced in whole or in part by voluntary hyperventilation. The Fourth International Symposium on Respiratory Psychophysiology discussed hyperventilation syndrome and attempted to settle on a definition, but this definition has been questioned (19). The hyperventilation test was found to be invalid as a test for the problems diagnosed as hyperventilation syndrome, and instead Howell suggested the term behavioural breathlessness (20); still, the dispute about the diagnosis of hyperventilation syndrome has continued (21, 22). Dysfunctional breathing is another example of the introduced diagnoses to describe patients with non-asthmatic divergent breathing patterns and breathing problems (23, 24).

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The descriptions of symptoms overlap, to a great extent, in the syndromes described above, and the lack of objectively measurable physiological findings has been problematic. It is not easy to assess asthma and other respiratory symptoms with questionnaires alone, and it is important to be aware of the need for validation of such tools when they are used in scientific studies (25).

A study with controlled perfume provocation in odour intolerant patients showed that the symptoms that these patients experienced after odour exposure could be induced even when the subjects could not detect any smell (26). Another finding was that patients with odour sensitivity and airway symptoms demonstrated increased cough reaction to inhaled capsaicin, compared both to healthy subjects and to patients with asthma (27). It was also shown that it is possible to block both symptoms and cough response from capsaicin inhalation test with a pre-inhalation of lidocain (28). We have chosen to focus on patients with symptoms from the upper and lower airways related to odour and pungent exposure, and to develop an objective test – the capsaicin inhalation test – to study this field (I, III).

## Prevalence of odour intolerance

Although intolerance to odours and pungent substances is a frequently reported problem in industrialized countries, before 1995 no one had studied its prevalence in a general population. A questionnaire has been developed as a research tool for investigating this problem, although its authors emphasized the difficulties inherent in using questionnaires to distinguish between asthma and chemical sensitivity (29).

The prevalence of chemical sensitivity was assessed in a telephone survey conducted in North Carolina, where 1446 households in a rural area were selected randomly. Allergy was diagnosed from the questionnaire as "becoming sick from exposure to natural things", and chemical sensitivity as "becoming sick after smelling chemical odours". According to these definitions, 35% of respondents reported allergy and 33% reported some degree of chemical sensitivity. One third of those reporting symptoms of chemical sensitivity said that it happened at least once a week (30).

In a similar telephone survey among a more urban population in Californa, in which more than 4000 adults participated, 16% of the respondents reported that they were "allergic or unusually sensitive to everyday chemicals". In this population, 6% had been diagnosed by a doctor with MCS or enviromental illness; but, surprisingly, nearly half of them did not report any sensitivity to chemicals, and the authors could find no explanation for this. Furthermore, among the 11% who reported asthma, 19% reported

doctor-diagnosed environmental illness or MCS as compared to 4.6% in non-asthmatics (31).

Another population-based questionnaire study investigated symptoms in patients with asthma, allergic rhinitis, and odour intolerance. Chest tightness as well as upper and lower airway symptoms were common among patients with odour intolerance. Asthmatics reported often feeling ill from some odours and non-asthmatics from others. Individuals with chemical sensitivity reported often asthma and a borderline significance for increased chemical sensitivity among asthmatics compared to non-asthmatics was also found (32).

A later postal survey of the population in the south of Sweden showed that 10% of the respondents reported annoyance from the smell of chemicals and 13% annoyance from other smells. There were indications of a minor influence on subjective physical and mental well-being in the group who reported annoyance from odours (33). When comparing groups of individuals annoyed by smell, individuals annoyed by electricity, and a control group, those annoyed by electricity showed strongly elevated scores within the anxiety/neuroticism dimension, while those annoyed by smell had a slight elevation on only one anxiety scale (34).

In a population study, with a random sample of more than 1000 individuals, conducted in the continental United States using a telephone questionnaire, 14% of the respondents were diagnosed with asthma and 11% reported being hypersensitivity to chemicals. Of those with asthma, 27% also reported being hypersensitive to chemicals and 7% were also diagnosed with MCS (35).

The quality of these studies varies, and they raise questions regarding recruitment bias and the accuracy of the questionnaire-based diagnoses of allergy, asthma, and chemical sensitivity. In addition, none of them evaluated the possible effect on chemical sensitivity of changes in the sense of smell. The findings of high prevalence of chemical sensitivity among asthma patients in several studies are evident. However, the telephone survey studies often report a very high asthma prevalence; and if asthma is overdiagnosed, it is difficult to assess the prevalence of chemical sensitivity among asthmatics. In all, this points to a need for additional research. The present thesis addresses this need with a population-based study in which symptoms were recorded via a structured interview together with an assessment of the sense of smell (II), and an investigation of the relationship between airway sensory hyperreactivity (SHR) and asthma (IV).

## Symptoms in individuals with odour intolerance

Patients who report odour intolerance often also complain of having a stuffy nose, itching in the upper airways or in the ears, eye irritation, hoarseness, cough, dyspnoea, or a feeling of blocked airways in the larynx region. When it comes to mucosal reactions after exposure to perfume and other fragrance products, symptoms in the upper airways are more common than those in the lower airways. Sensitive individuals also sometimes report pressure over the chest and even chest pain accompanied by general symptoms like headache, perspiration, vertigo, and tiredness (18, 26, 36, 37). Some of these patients have been mistakenly diagnosed with asthma, e.g. those who report breathing trouble and chest discomfort after exercise without having either asthma or signs of other obstructive lung disease (38).

In a five-year study of the prognosis of patients with airway odour sensitivity in combination with increased capsaicin sensitivity, the severity of symptoms remained constant and was related to low quality of life (39).

Different strategies are required to allow patients with these symptoms to cope in daily life. The feeling of being socially handicapped is intensified by other people's lack of understanding, despite the fact that sensitivity to odours and chemicals is common within the population. In addition, patients are often concerned that the symptoms will transition into a serious disease (40).

In accordance with the discussion above, we chose a questionnaire that is not constructed to assess the symptoms, but to measure the affective reactions to and behavioural consequences of chemical sensitivity, CSS-SHR (41). CSS-SHR is a shorter version of the Chemical Sensitivity Scale (CSS) (42, 43). Since the symptoms in individuals with odour intolerance without allergy or asthma have been a matter of debate, we also included other aspects of symptomatology in the investigations (I-IV).

## Innervation of the airways

The main physiological function of the upper airways is to guarantee the quality of inhaled air, and so mechanisms to warm and humidify the inhaled air and to protect the lower airways from inhaled particles and toxic substances are important. Airway reactions to chemical stimuli are essential protective physiological mechanisms against the inhalation of harmful substances. These functions require an afferent sensory nervous system, the common chemical sense, to register the temperature, the humidity, and the quality of inhaled air (44). Both the trigeminal (ophthalmic, maxillary, and mandibular nerve) and the glossopharyngeal nerve are involved in the afferent

innervations of upper airways, and the vagal nerve plays a similar role in the lower airways. The afferent nerves contain A-fibres (e.g. Aδ-fibres) and unmyelinated C-fibres that branch through the basal membrane near the tight junctions between the epithelial cells. The protective physiological mechanisms of the airways also require the efferent nervous system to regulate secretion in the nose, mucosal swelling, and pharyngeal and laryngeal function. Irritation of mucous membranes in the nose can result in bronchial constriction, but it is not known whether this reflex mechanism is mediated through cholinergic or non-cholinergic parasympathetic systems (45, 46). The innervations of the airways, immunological reactions in the upper and lower parts of the airways, and known connections give us a basis for the concept of the united airway (44, 47).

Together with the common chemical sense, the sense of smell plays an important role in the physiological system protecting us from inhalation of harmful substances. The sense of smell has been viewed as a low-threshold warning system, and the common chemical sense as a high-threshold one, but the actual situation seems to be more complicated. Repeated administration of n-butanol results in adaptation to smell but not to perception of the irritating stimulus (48). The range of thresholds for olfactory and trigeminal stimuli (irritants) is wide for some substances and narrow for others. For the majority of chemicals that have been investigated, the olfactory threshold is sufficiently lower than the irritant threshold to provide a warning signal before the onset of irritation (49). These thresholds can be studied using a method developed on the basis that trigeminal but not olfactory stimulus can be localized to the left or right side of the nasal mucosa (50). Another method is to study trigeminal threshold in anosmic individuals by comparison with healthy controls (9, 51). A study of anosmic individuals, hyposmic individuals, and healthy controls showed a lower trigeminal threshold in those with olfactory dysfunction than in healthy controls, and a decrease in trigeminal sensitivity with age (52).

Research into airway sensory nervous system and sensory receptors has given new insights about the interactions between inhaled air and the airways, and the mechanisms are now better understood (53-56). A certain group of airway sensory receptors (TRP channels) belongs to the voltage-gated-like ion channel family. These receptors have, for example, the ability to sense temperature, pain, stretch, and osmolarity, and they seem to be important for the interaction between environment and respiratory system. They also have important functions in other organs. The receptors are built up from proteins forming tetramers with a central pore and a characteristic amino acid sequence that can control the flux of a specific ion ($Na^+$, $K^+$, $Ca^{2+}$, or $Mg^{2+}$) through the cell membrane. This function can be modified by other proteins (57, 58).

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The TRPV-1 receptor (transient receptor potential channel, vanilloid receptor 1) is a receptor for capsaicin (59). Capsaicin is the odourless major pungent ingredient in chilli fruits, and belongs to a well defined group of vanillylamides (60). Inhalation of capsaicin causes cough in the lower airways and a hot burning sensation in the upper airways (61, 62) by stimulating a population of afferent neurons, most of them C-fibers but even some Aδ-fibers (61, 63). Other receptors for capsaicin in the central nerve system have been postulated (64). The TRPV-1 receptor is found in nerve endings in the upper and lower airways, and it can even respond at temperatures of ≥42°C, to protons (acids) and also to a series of endogenous lipids. The clinical importance of this receptor has yet to be evaluated, but one interesting finding is that mucosal injury (which is a cause of local low pH in the tissue) can lead to increased expression of TRPV-1 receptors. The C-fibres in the upper airways of both animals and humans contain neuropeptides (e.g. SP and CGRP). Neurogenic inflammation through axon reflexes with the release of neuropeptides has been demonstrated in both upper and lower airways in rodents (65), but it is questionable whether this occurs in the lower airway in humans and there is only a little evidence for it in the upper airway (66). However, the secretion of nerve growth factor (NGF) in the nose increases after capsaicin provocation of lower airways in patients with airway odour sensitivity. It is not yet known whether this is caused by a reflex mechanism or a direct effect of capsaicin on the nose cavity (67).

The response to capsaicin in the airways can be blocked both by lidocaine (68) and by capsazepine. Capsazepine is a synthetic analogue of capsaicin, and acts as a competitive antagonist (69). In guinea pigs, the specific TPRV-1 inhibitor, V112220, a pyridazinylpiperazine analogue, significantly inhibits the number of coughs induced by both citric acid and capsaicin compared to controls (70).



Capsaicin                                    Capsazepine
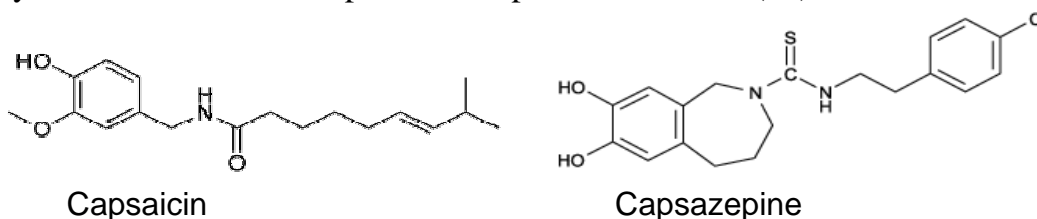
The TRP families represent a complex system of receptors in the airways, and it is an interesting finding that some patients with symptoms from upper and lower airways after exposure to odours and pungents have increased response to the capsaicin inhalation test. This could be the result of increased expression of TRPV-1 or a closely linked protein and this is the reason for the development of a capsaicin inhalation test for diagnostic purposes (I, III).

## Objective verification of odour intolerance

Over the years, there has been much dispute about the pathophysiology of chemical sensitivity, but only a few provocation studies have been performed. In a systematic review of 37 studies regarding chemical intolerance (71), only six were blinded, and one of these was of chronic fatigue syndrome, which is of limited interest for investigation of odour intolerance with airway symptoms. Four of the blinded studies showed some positive results. In one of them, MCS patients underwent airway provocation with the chemicals that they had reported symptoms from. The participants could sometimes identify the stimuli, but the symptoms could not be reproduced when the provocations were double-blinded (72). However, in another study, subjects with MCS who were provoked single-blinded showed no difference regarding sensations of smell or development of CNS-related symptoms compared to a control group, but had significantly higher subjective rating of symptoms related to irritation (i.e., eyes, nose, throat, skin, and breathing difficulties) (73). In another study subjects with chemical sensitivities took longer than controls to adapt to baseline in the protocols of some physiological measurements. After adaptation, cases displayed statistically significant responses in tonic electrodermal response to test substances, both compared with controls and compared with the control substance. Symptoms were also higher in cases than in controls for body wash solution and dryer sheets (74). In two other studies, subjects with odour sensitivity were provoked with perfume in the lower airways or the eyes; they showed symptoms even when the nose was blocked so they could not sense smell during the experiments. These findings suggest a hyperreactivity of the respiratory tract induced by a trigeminal reflex via the airways or the eyes (26, 75).

The conclusion in the review of Das-Munshi et al. was that people with MCS do react to chemical challenges, but that these responses occur only when they can discern differences between active and sham substances; this suggests that the mechanism of action is not specific to the chemical itself, but might be related to expectations and prior beliefs. However, these conclusions must be viewed with an understanding of the heterogeneity of the patients included in the MCS syndrome, and may not be relevant for all patients, as several studies concerned individuals with symptoms other than those from the airways. Some of the studies do not support the idea of a connection between the symptoms of odour sensitive patients and olfactory stimulation related to expectations and prior beliefs, but until now too few patients have been studied. The present thesis focuses on the group with mainly airway symptoms after exposure to odours and pungents (I-IV).

## Development of the capsaicin inhalation test

The finding that individuals with odour sensitivity had increased sensitivity to capsaicin inhalation (27) motivated the development of a capsaicin inhalation test for diagnostic purposes (I, III).

Different provocation tests for the airways have been developed in order to study cough reactions in different airway diseases, and to test various cough medications. Capsaicin and citric acid have often been used to induce experimental and pathologic cough response in humans, but citric acid seems to give more problems with the performance of the test and the reproducibility of the results (76, 77).

Capsaicin produces a dose dependent cough response after inhalation of incremental concentrations with no tachyphylaxis, or only a partial and temporary one. The response is an effect of stimulation of both the larynx and more peripheral airways (61, 68, 77, 78). After capsaicin inhalation, patients with odour sensitivity experience dyspnoea, upper airway symptoms, and eye irritation (28). Inhaled lidocaine blocks not only the cough (68, 77, 79), but also the dyspnoea and other airway symptoms induced by capsaicin in patients with odour sensitivity (28).

Provocation tests with inhaled capsaicin can be performed with different protocols, either to define the threshold concentration for coughing two or five times (C2 and C5, respectively), or to measure the cough response after inhalation of a fixed concentration (68, 77, 78, 80). Both methods have advantages and limitations. The fixed concentration method and the C5 threshold method both have good short-term reproducibility when used in appropriate populations, but a carry-over effect is seen after provocation with a high concentration if the tests are performed in a randomized order (77, 81). Long-term reproducibility has also been studied, and has been found sufficient for both methods (39, 81). It is important to realize that these methods do not measure exactly the same physiological effect. Both methods measure the response after the sensory signals have passed the filter in the brain and given the efferent signal to cough; however, the threshold method measures the threshold for coughing while the fixed concentration method measures the total response of cough after an inhalation of a concentration above the threshold. Individuals with increased airway sensitivity often cough even after inhalation of saline, which is a serious drawback of the threshold method in this patient group (27, 82). The inhalation equipment is important for the results, and normative data must be analyzed for the method in use (83).

A safety investigation covering 20 years of clinical experiences of provocation tests with inhaled capsaicin showed no serious adverse event in humans (84).

Given the known sensitive cough reflex in some patients with odour intolerance, the threshold method did not seem to be appropriate for SHR-patients. Therefore, in order to develop normative data for a capsaicin inhalation test in patients with odour intolerance, we chose the fixed concentration method (I, III).

## Capsaicin sensitivity– relationship to other diseases, smoking, and gender

Atopic patients who suffer from airway symptoms after exposure to odours and pungents have increased sensitivity to inhaled capsaicin compared to atopic patients without airway symptoms after exposure to odours (85). In asthmatics with birch pollen allergy, sensitivity to capsaicin increases during pollen season (86). However, atopic patients without asthma did not have increased capsaicin sensitivity (87), nor was there a correlation between cough threshold and the methacholine test; this suggests that cough sensitivity and bronchial responsiveness may be independently potentiated by different mechanisms in chronic airway inflammation (88). Another study of patients referred to an allergy clinic because of lower airway symptoms showed no relationship between capsaicin test and methacholine test (89). On the other hand, increased capsaicin sensitivity was found to be an important contributor to the presence of cough in both asthma and chronic obstructive pulmonary disease (COPD). No relationship between capsaicin responsiveness and airflow limitation was found, and therefore the mechanisms behind coughing are likely to be different from those causing airway obstruction, at least in patients with COPD (90). The findings regarding augmented capsaicin sensitivity in asthma patients were claimed to be due to cough variant asthma in a subgroup of the patients, since asthmatics without cough did not show such an increase (91).

Sensitivity to inhaled capsaicin is augmented in a number of chronic pulmonary conditions with cough as a major symptom; for example, lower airway conditions such as COPD (90, 92) and cystic fibrosis (93), and also cryptogenic fibrosing alveolitis/idiopathic pulmonary fibrosis (94, 95). Airway sensitivity to inhaled capsaicin increases during respiratory infections (96), but is lower among smokers than among non-smokers (97, 98); the second of these findings is consistent with the hypothesis that nicotine inhibits or blocks the C-fibres of the sensory nervous system of the lower respiratory tract (99).

Cough sensitivity is higher in females than in males (100, 101). Other parameters such as height, weight and lung function have been shown to have no major influence on the outcome of capsaicin provocations, and hence the disparity between males and females may be regarded as due to a true sex difference (102).

However, one study of a group of patients with chronic cough showed no gender differences in capsaicin sensitivity (80).

Given this evidence for relationships between capsaicin sensitivity and gender and smoking, we were motivated to study these factors in relation to odour sensitivity (II - IV). In addition, the disparity of opinions about the relationship between capsaicin sensitivity and asthma confirmed the importance of elucidating the relationship between SHR and asthma (IV).

# Aims of the thesis

The general aims were:

- to study the relationship between odour intolerance and capsaicin sensitivity and to develop a definition SHR.
- to study epidemiology of odour intolerance; particularly regarding airway symptoms, and to relate odour intolerance to possible risk factors.
- to investigate the relationships between SHR and other respiratory diseases.
- to study psychiatric morbidity at SHR.

## Study I

The aim of study I was to establish the capsaicin inhalation test in patients with pronounced odour intolerance, in comparison to healthy individuals and patients with other airway symptoms.

## Study II

The main aim of study II was to determine the prevalence of self-reported general odour intolerance, and the prevalence of such sensitivity that has affective and behavioural consequences for the individual. Other aims were to determine the type and severity of the symptoms induced by odorous/pungent substances; to relate odour intolerance to possible risk factors such as sense of smell, gender, and smoking habits; and to obtain normative data for the CSS-SHR.

## Study III

The aim of study III was to determine the relationship between self-reported odour intolerance and capsaicin sensitivity, and to estimate the prevalence of SHR, defined as a combination of odour intolerance with affective and behavioural consequences and a pathological capsaicin test. A secondary aim was to evaluate, whether the order of administrated capsaicin had any effect on the response.

## Study IV

The primary aim of study IV was to clarify whether there is a relationship between SHR and asthma, and to study the influence of smoking. The secondary aim was to study whether SHR patients show signs of increased psychiatric morbidity.

# Subjects and Methods

## Subjects

The studies included a total of 2847 adult individuals, 897 of whom were patients. Of these, 2252 eventually participated. Women were slightly overrepresented (55%). Studies I and IV were performed among patients referred to the Allergy Centre at the Central Hospital of Skövde. Study IV also included a group of asthma patients from three Care Centres. Study II was a cross-sectional, population-based epidemiological study of adult inhabitants in Skövde, and in study III randomly selected individuals from this population-based study were further investigated.

## Ethical aspects

Informed consent was obtained from all participants. All studies were approved by the Regional Ethical Review Board of Gothenburg, Sweden; Dnr L 147-99 (I), Dnr Ö 452-00 (II), Dnr Ö 616-02 (III), Dnr 239-06 (IV).

## Questionnaires

Questionnaires were used to evaluate the symptoms and their consequences for the participants' social lives (I-IV). In study I, we evaluated sensitivity to the odours of

chemical substances such as perfumes, cleaning agents, flower scents, tobacco smoke, and car exhaust fumes; we also evaluated the social effects of sensitivity to odorous substances. In later studies we used the CSS-SHR, a validated questionnaire on the affective and behavioural consequences of odour sensitivity (41) (II-IV). In study IV we also included the Hospital Anxiety and Depression Scale (HAD), a validated instrument for investigating signs of depression and anxiety in patients (103-105), and made use of a questionnaire for classifying asthma severity into four groups by symptoms and medication, in accordance with the GINA guidelines (106).

## Capsaicin inhalation test

A nebulizer (Pariboy 36; Paulritzau Pari-werk KG; Starnberg-am-See, Germany) was used to administer inhalation of aqueous dilutions of an odourless capsaicin solution prepared from a stock solution of capsaicin. The number of coughs was registered and counted for 10 min from the start of provocation. The test was initiated with the inhalation of l ml of saline for 6 min, in order to teach the inhalation technique to the participants. This was followed by 4 min of rest, and then the individuals were provoked in the same manner with doses of capsaicin (0.4, 2.0, and 10.0 µM). The 10.0 µM capsaicin solution was later excluded due to experiences of excessive coughing and interrupted provocations on this concentration (III, IV). The cut-off for a positive capsaicin inhalation test, primarily defined in study I and further discussed in study III, was finally defined as 35 coughs after provocation with a concentration of either 0.4 or 2.0 µM capsaicin. The exclusion criteria for the capsaicin provocation test were pregnancy and breast-feeding, and the provocation was not administered during an acute respiratory infection nor for the following three weeks.

## Methacholine test

The methacholine test was performed as described by Löwhagen (107). Methacholine chloride solution was nebulised in a nebulizer (Pariboy, output 0.8ml/min with continuous nebulisation) and inhaled by tidal breathing for 2 min. Methacholine was inhaled in doubling concentrations starting with 0.03 mg/ml to a maximum concentration of 16 mg/ml. $FEV_1$ was measured 30 and 90 s after each inhalation. The provocation was continued with 5 min intervals between inhalations until a fall in $FEV_1$ of 20% or greater was obtained; and the concentration of methacholine producing such a fall in $FEV_1$ ($PC_{20}$) was recorded. Treatment with inhaled $\beta_2$-agonists was ceased 6 h prior to challenge for short-acting $\beta_2$-agonists and 24 h prior to challenge for long-acting. A fall in $FEV_1$ of $\geq$20% after inhalation of a concentration of $\leq$4.0 mg/ml was regarded as a positive test (IV).

# Results

## Development of the capsaicin inhalation test for SHR

Patients with upper and lower airway problems who had been admitted for allergy testing (n=95) were grouped into those with SHR symptoms (n=15, 16%) and those without, and compared with healthy controls. All individuals reacted dose-dependently to the capsaicin inhalation test, and patients who scored high on the odour intolerance questionnaire reacted more than other patients and also more than healthy controls. The 95% confidence intervals for mean values of cough response after 2.0 and 10.0 µM did not overlap between patients and controls, and the limit values were thereafter set to 10, 35, and 55 coughs respectively (I). The cut-off for a positive capsaicin inhalation test was finally defined as 35 coughs after provocation with a concentration of either 0.4 or 2.0 µM capsaicin (III, IV).

Participants with a positive CSS-SHR score ($\geq$43) coughed more on average than others on the capsaicin concentrations of 0.4 µM (p <0.01) and 2.0 µM (p <0.0001). The order of inhaled capsaicin concentration was found to influence the results, and hence inhalation with increasing doses was recommended (III).

The capsaicin inhalation test was performed in a total of 345 individuals without any major adverse event.

SHR was defined as a combination of odour intolerance with affective reactions to and behavioural consequences of exposure (CSS-SHR $\geq$43) and a pathological capsaicin inhalation test (III).

## Epidemiology

The prevalence of intolerance to odorous and pungent substances in a general Swedish population was estimated with a structured interview including 1900 adults, 73% of whom completed the study (II). Self-reported odour intolerance was found in 33% of the participants, and was more common in women (OR=2.0, 95% CI: 1.6-2.5), but no increased risk was found related to age, smoking, or impaired sense of smell (measured with the Scandinavian Odour-Identification Test). Respiratory symptoms and current smoking were more common among patients with odour intolerance, but

were not related to either the total amount of smoking (pack-years) or BMI. The pattern of different types of symptoms showed that half of the 33% with self-reported odour intolerance reported light symptoms and the other half moderate or severe symptoms. More symptoms were reported from the upper than from the lower airways, and one-third of those complaining of odour intolerance reported other symptoms, such as headache and nausea (II, part 1). Odour intolerance with positive CSS-SHR was reported by 19% (95% CI: 15-22%) of 595 individuals. This was more common in women (OR=2.3, 95% CI: 1.5-3.6), but no increased risk was found in relation to age, smoking, or impaired sense of smell (II, part 2).

Study III demonstrated a relationship between capsaicin sensitivity and CSS-SHR score; 81% of those with a positive capsaicin inhalation test had a positive CSS-SHR score, and only 5% of those with a negative CSS-SHR score had a positive capsaicin inhalation test. The prevalence of SHR in a general Swedish adult population was estimated at 6% (III).
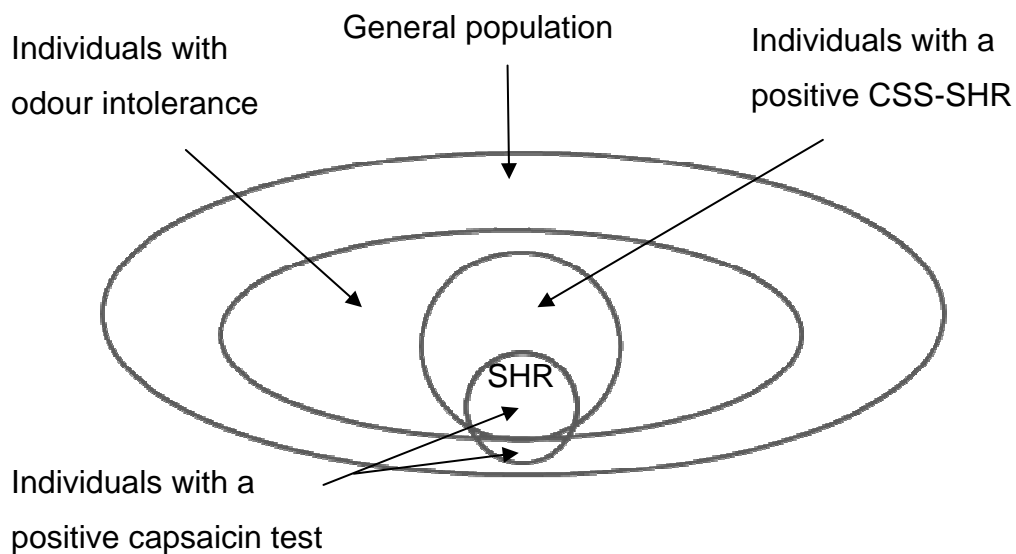


Fig. A positive capsaicin inhalation test was strongly related to odour intolerance, but a small group of individuals had a positive capsaicin inhalation test without a positive CSS-SHR score. In the great majority of people with odour intolerance, capsaicin sensitivity was normal (II- III).

In the group of patients referred to the Allergy Centre because of airway symptoms, SHR (diagnosed with a positive symptom score and positive capsaicin test) was related to female gender, rhinitis, and lower airway sensitivity to cold air; but not to age, asthma, or smoking (I).

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In 724 consecutive patients referred to the Allergy Centre, the prevalence of SHR was investigated in four subgroups. The prevalence among asthma patients was 6.4% (95% CI: 2.2-10.6) and that among patients with other airway symptoms was 8.8% (95% CI: 4.2-13.4). A lower prevalence was seen in the other two groups; "allergic rhinitis without asthma", and "no airway disease" (IV).

Asthma was no more common among patients with SHR than would be expected in the Swedish population (108-111), and there was no evidence that SHR is more common among asthma patients than in the general population (IV).

No relationship between SHR and smoking was found, but current smokers were uncommon in the study population (IV).

No relationship between SHR and depression was found, neither an augmented prevalence of "possible depression", according to the HAD scale, compared with data from general Swedish population (112). Similarly, we found no signs of increased "possible anxiety or depression" (according to the HAD scale) in SHR compared to asthmatics and other patients with a positive CSS-SHR-score, who had been referred to the Allergy Centre (IV).

# Discussion

The recognition of a group of patients whose symptoms are not in accordance with any general accepted diagnosis is a significant challenge, both in clinical practice and in research. In the early phase of these studies, the lack of validated tools in this area of research was indeed problematic. Problems in the attempts to define a disease are not uncommon in medical science. One example is the development of the diagnosis of bronchial asthma; after a decade of progress in diagnostics and treatment, the diagnosis has again been questioned (113, 114). The development of scientific knowledge was described in 1935 by Ludwig Fleck in the monograph ´Entstehung und Entwicklung einer wissenschaflichen Tatsache. Einführung in die lehre von Denkstiel und Denkkollektiv´(115, 116). This work had almost been forgotten, when in 1962 Thomas Kuhn referred to it as "an essay that anticipates many of my own ideas". Kuhn's analysis of changes in science in the monograph ´The Structure of Scientific Revolutions´ obtained wide recognition, and the term "paradigm" for Fleck´s term "Denkstiel" has often been used (117). Fleck was trained in medicine, and his ideas can easily be applied to medical research. The development of the Wasserman reaction, with small steps being taken in interaction between several research groups and re-evaluation of findings in the light of new knowledge (115, 116), has indeed some similarity to the ongoing research into odour intolerance and the description of airway sensory hyperreactivity. It is not possible to use validated methods at the beginning of a research project of this type, but with increasing knowledge the validation improves, and sometimes new interpretations of results are necessary. Often this can be done within the same paradigm (Denkstiel). To be accepted as a paradigm, a theory must explain the facts better than the competing thories, even if it does not explain all known facts (117). The proposed diagnoses of dysfunctional breathing for patients with otherwise undiagnosed breathing problems, and MCS or IEI for individuals with chemical sensitivity, have neither been generally accepted nor been replaced by other diagnoses. There is still no generally accepted paradigm which explains the disease in these patients.

In this thesis, we have focused on a group of individuals who experience airway symptoms and sometimes general symptoms after exposure to concentrations of odours and irritating chemical substances which are normally regarded as non-toxic. Most of these individuals regard themselves as suffering from a disease; however, the symptoms may be a reaction to a society overloaded with different fragranced products, and could be seen simply as one extreme of normal variability. These symptoms have often been explained as a supposedly augmented psychiatric vulnerability (6, 14, 15). However, the findings that symptoms could be induced by

single-blinded perfume provocation, the increased sensitivity to capsaicin in the airways in a group of such individuals, and the blockage of both symptoms and cough response of capsaicin inhalation after double-blinded lidocain inhalation, strengthens the hypothesis of another pathophysiology (26-28, 75, 118).

We started by establishing limit values for a capsaicin inhalation test in patients with airway odour intolerance in comparison to control subjects (I). This knowledge was used to develop the CSS-SHR questionnaire, which was aimed at evaluating the affective reactions to and behavioural consequences of the symptoms instead of trying to measure the symptoms themselves (41). This is important since sensitive individuals may change their behaviour due to the symptoms. Some individuals with increased sensitivity may avoid exposure, and hence do not suffer from symptoms, while others may choose to take part in social life even at the cost of exposure and consequent symptoms. In the population-based study, a relationship was established between CSS-SHR score and capsaicin response. With the use of the capsaicin test and CSS-SHR, we were able to distinguish a group of individuals characterized by a validated questionnaire and a measurable physiological finding. For this group, we propose the diagnosis of SHR (III).

Although SHR has measurable characteristics, there are still unsolved problems. For example, 20% of individuals with a positive capsaicin inhalation test do not have a positive CSS-SHR score. This result can be interpreted in different ways. One possible explanation is that the questionnaire has a low sensitivity; however, this does not seem likely in the light of the fact that 19% of the population have a positive CSS-SHR score. If the questionnaire has enough sensitivity, then there must be other explanations. It may be that capsaicin sensitivity is linked to odour intolerance without a direct causal connection, or it may be a matter of the timetable for the development of this syndrome; the increased capsaicin sensitivity may develop before any symptoms are experienced, or sometimes the opposite may be the case. It is also important to remember that cough sensitivity to capsaicin may be augmented in other lower airway conditions, such as COPD (90, 92), cystic fibrosis (93), and idiopathic pulmonary fibrosis (94, 95).

Another question is how to explain the odour intolerance in individuals without a positive capsaicin inhalation test. As many as two-thirds of individuals with odour intolerance and a positive CSS-SHR score belong to this group (III). This result may be partially explained by the fact that the cut-off for pathologic capsaicin inhalation test was set with the aim of achieving high specificity, which resulted in a lower sensitivity. It is also important to remember that upper airway symptoms are more common than lower airway symptoms among individuals with odour intolerance, and

our present test system actually tests sensitivity in the lower airways. We also think that the group which reports odour intolerance is a heterogenic group, and so different mechanisms may be involved. Many of these individuals have no airway symptoms, but instead report more general problems such as headache and nausea. The CSS-SHR is not focused on airway symptoms, and it may have both advantages, regarding coping strategies (discussed elsewhere), and disadvantages, in its nonspecificity. Even if chemical sensitivity can be found in anosmic individuals, the complex interaction between the olfactory and the trigeminal system may be of importance (10). Our strong memory of odours, often connected to positive or negative experiences, gives a plausible background for psychological reactions.

New findings may change the general opinion of a disease, and recent research regarding airway sensory receptors gives us a new view of the situation. In recent years there has been an increasing interest in the family of TRP ion channels, which are able to sense conditions including temperature, noxious stimuli, stretch, osmolarity, and pain, and which may be involved in different diseases via an increased level of channel expression (58, 119, 120). The TRP ion channels are important for multiple organ systems in their interaction with the environment. Patients with chronic cough showed a significant correlation between cough response to capsaicin and the number of TRPV-1 positive nerves in airway mucosa (121), and the expression of TRPV1 is also upregulated in the smooth muscle of the airways in these patients (122). The complexity of the TRP receptor system may explain why so many individuals with odour intolerance have a negative capsaicin test and why some with a positive capsaicin test do not have symptoms; however, it is also possible that other mechanisms are involved.

The psycho-neurological processing of chemosensory information varies between individuals, and mechanisms other than variations in the receptor system may of course be important for the development of symptoms (123). In a recently published study of mice, an interaction was found between exposure to odorous sulphur-containing substances and the response to capsaicin with increased response to capsaicin after exposure to the odours. This interaction may be one explanation for the findings of a connection between odour intolerance and increased capsaicin sensitivity (III) (124). If this can be reproduced in humans, it could help to explain the pathophysiological basis for odour intolerance and SHR. Another recent study tested the hypothesis of an association between capsaicin cough sensitivity and sensitivity to $CO_2$ with respect to detection sensitivity and electrophysiological brain response. The results imply that capsaicin cough sensitivity, such as in SHR, is related to a higher detection sensitivity, and tends to be related to faster cortical processing of other chemosomatosensory substances, at least of $CO_2$ (125).

PET scan has been used as a method of visualizing dynamic changes in metabolism. A study of regional cerebral blood flow with PET scan showed that individuals with MCS process odours differently from controls; however, this occurs without signs of neuronal sensitization. One possible explanation for the observed pattern of activation in MCS is a top-down regulation of odour-response via the cingulate cortex (126). This finding is difficult to interpret, as it could result from either psychological reactions or changes in the airway sensory system in this patient group.

Some studies report that chemical sensitivity is linked to psychiatric morbidity (6, 14), and several studies have demonstrated a relationships between asthma and anxiety or depression (127-129). The SHR patients in study IV did not show augmented prevalence of "possible depression" (according to the HAD scale) compared with data from the general Swedish population (112). Sign of increased prevalence of "possible anxiety or depression" (according to the HAD scale) in SHR were not shown, when we, in the Allergy Centre population, compared patients with SHR to patients with asthma and other diagnoses with a positive CSS-SHR score, or compared to what was earlier found in an adult asthma population (128). The results do not support the theory that psychiatric morbidity is a major cause of SHR. However, the number of patients was limited; further studies in this field are needed. Our results cannot unreservedly be generalised to other groups of patients with chemical sensitivity, for example those with MCS.

Our results could indeed be interpreted as changes in the psycho-neurological processing of the afferent stimuli from the airways after certain exposure; but the few provocation studies in SHR patients, the correlations between symptom score and response in the capsaicin test, the finding of changes in response regarding nerve growth factor in nasal lavage fluid after capsaicin test in SHR patients, the lack of signs of psychiatric morbidity in SHR patients, and our general experience of the patients, all speak in favour of the proposed diagnosis of SHR and of a peripheral somatic pathophysiology for this disease (I, III, IV) (26, 67, 75).

Odour intolerance is a common problem, and our results regarding the prevalence of odour intolerance in a general Swedish population are in accordance with those of other studies (30-33, 130). Like others, we found that odour intolerance is more common in females (II, III) (30-33, 130). There is no obvious explanation for this. In study III, one-third of the individuals with positive CSS-SHR had a positive capsaicin inhalation test, both among men and among women. This result could support the idea that there is a direct linkage between odour intolerance and capsaicin sensitivity which is not correlated with sex differences.

Chemical sensitivity seems to be increased in at least some groups of asthma patients (32, 35, 37), and capsaicin sensitivity is also more common in asthma patients (91); however, we found no evidence for SHR being more prevalent in asthmatic patients than in the general population (IV). Our results cannot rule out the theory that SHR is more common in asthmatics, but there is no obvious relationship, and our results do support the idea that SHR has a different pathogenesis than asthma. On the other hand, since both conditions are common, there ought to be several patients with both asthma and SHR. This interaction may result in diagnostic difficulties and a risk of overmedication of symptoms in asthma patients.

A study of the prevalence of SHR in teenagers showed considerably lower prevalences of odour intolerance, positive CSS-SHR scores, and SHR (1%) than in adults (131). These findings indicate that SHR is an acquired disorder. It must be asked whether exposure to odours and pungent substances causes this disease, or whether it merely induces the symptoms. Toxic effects and gene-environment interactions are indeed important to consider as possible causes of the disease. As is the case with MCS, SHR patients are likely to regard themselves as having been injured by the particular exposure that accompanied the onset of problems. Today, we have no definite knowledge regarding such connections, and this is important to remember, when we are answering insurance questions.

With our definition of SHR, we have described a disorder with a validated questionnaire and a measurable physiological test. This definition cannot include all patients with odour intolerance or chemical sensitivity, nor can it include all patients with MCS, IEI, or dysfunctional breathing, even though a proportion of patients with MCS have a positive capsaicin test (132). Our present definition of SHR is chosen to give high specificity, which will result in few false positives but probably more false negatives. This is important to remember, not only when it is used as a research tool, but also when it is used in clinical practice. The development of the Wasserman reaction to a medical success is now history. Other methods are in use, and the Wasserman reaction is regarded to have too low a specificity for today's standards. The asthma diagnosis is questioned, although the progress in that field has resulted in the development of good treatment for most cases. This thesis is concerned with a new field of research, and our methods will undoubtedly be replaced by others with higher sensitivity and specificity; still, we have taken what we hope are only the first steps towards a better understanding of patients with odour intolerance.

# Conclusions

Intolerance to odours is a common phenomenon in the Swedish population, and there is a considerable group of individuals in which airway odour sensitivity is linked to an increased capsaicin cough sensitivity. This is more common among women than among men. A high score on a questionnaire measuring the affective and behavioural consequences of odour intolerance, in combination with a positive capsaicin inhalation cough test, represents a distinct clinical entity. For this group of individuals, we propose the diagnosis of airway sensory hyperreactivity (SHR). The capsaicin inhalation test was developed in several steps, to establish normative data and cut-off values.

SHR was no more common in asthmatic patients than in the general population, and asthma was no more common in SHR patients than in the general population. The number of patients included in our study was small, and the results must be interpreted with caution. Although the symptoms of SHR and asthma are often confused, there is no obvious connection between the two conditions. We have not found evidence for the hypotheses that SHR is related to sense of smell or smoking habits, nor for the theory of psychiatric morbidity as a major cause of this disease.

# Perspectives for the future

Controlled provocation studies with various irritating substances are needed to increase our understanding of the nature of this type of reactions. A strict definition of the patient group is essential for interpretation of provocation tests and comparison with controls. Methods developed to distinguish olfactory and trigeminal responses could help us understand the mechanisms behind the results of the provocations. Studies of EEG-related responses in the cortex (event related potentials, or ERPs) after sensory stimulation of the upper airway are promising in this field.

Investigation of the airway sensory receptors (e.g. the capsaicin receptor TRPV-1) has given new insights into the interface between inhaled air and the airways, and further studies in this field could be a key to the underlying pathophysiology of SHR. The capsaicin inhalation test may be useful in these studies. More knowledge of pathophysiology and pathogenesis will increase the possibility of finding methods for prevention and treatment of the disease.

# Acknowledgement

I would like to express my sincere gratitude to all the people who have contributed to this project. In particular I will acknowledge:

# Summary in Swedish –
# Populärvetenskaplig sammanfattning

Vid exponering för dofter och luftburna kemiska ämnen uppstår hos somliga personer symtom som t.ex. tungandning, tryck eller tyngdkänsla över bröstet, hosta, slembildning, heshet, snuva, nästäppa och ögonirritation. Svettningar, trötthet, yrsel och huvudvärk rapporteras också. Denna till synes ökade känslighet för doftande ämnen och kemikalier leder inte sällan till problem både i arbetsliv och på fritid. Vid utredning finner man ofta varken allergi, astma eller annan känd sjukdom. Läkemedel mot astma och allergi har inte heller någon effekt. Detta tillstånd har bl.a. benämnts multipel kemisk överkänslighet (multiple chemical sensitivity, MCS) och funktionell andningsrubbning. Innan man 1998 påvisade en stark koppling mellan sådana symptom och en ökad känslighet i luftvägarna för inandad capsaicinlösning saknades sätt att mäta någon störning i kroppsfunktionerna hos dessa personer. Capsaicin är det starka men luktfria kryddämnet i spansk peppar. Det kan tillredas i exakt angivna spädningar för testning. Det har emellertid funnits ett behov av gränsvärden för capsaicintest vid undersökning av denna patientgrupp.

Avhandlingen har som syfte att bestämma gränsvärden för capsaicintest, att definiera begreppet sensorisk hyperreaktivitet i luftvägar (SHR) utifrån symtom samt känslighet vid capsaicintest och att beskriva förekomsten av dessa problem i befolkningen. Slutligen skall sambanden mellan SHR, luktsinne, tobaksrökning och astma undersökas samt betydelsen av förekomst av ångest- och depressionsbenägenhet för SHR belysas. Som grund för detta har 4 delarbeten genomförts. Dessa har efter prövning godkänts av regionala etikprövningsnämnden i Göteborg.

Syftet för studie I var att etablera gränsvärden för capsaicintest hos patienter med luftvägsbesvär utlösta av dofter och kemikalier. 95 patienter, som remitterats för allergiutredning undersöktes genom provokationer med inhalation av capsaicin i stigande koncentrationer. Antalet hoststötar registrerades, relaterades till luftvägssymptom och patienter med och utan doftkänslighet jämfördes med en grupp friska individer. Hos alla försökspersonerna uppstod en dosberoende reaktion i form av hosta vid inhalation av stigande koncentration capsaicin. Gränsvärden för ökad känslighet vid capsaicintest bestämdes till 10, 35 respektive 55 hoststötar vid koncentrationsstegen 0.4, 2.0 och 10 µM capsaicin. De uppsatta gränsvärdena för capsaicinkänslighet analyserades vidare och kunde förenklas till ett värde. Om man reagerar med ≥35 hoststötar efter inhalation av 1 ml 0.4 eller 2.0 µM capsaicinlösning har man en ökad känslighet och testet bedöms som en positiv capsaicintest.

I studie II undersöktes förekomsten av självrapporterad känslighet för dofter och kemikalier, vidare förekomsten av sådan känslighet som medförde att personernas beteende påverkades. Dessutom studerades om rökvanor eller förändrat luktsinne har betydelse. Av ett slumpmässigt urval av 1900 vuxna invånare i Skövde från olika åldersgrupper angav 33% viss doftkänslighet medan 19% hade doftkänslighet av sådan grad att detta påverkade personerna emotionellt och socialt. Förekomsten var dubbelt så hög hos kvinnor som hos män men förändrat luktsinne eller rökvanor tycks inte påverka förekomst av doftkänslighet.

I studie III påvisades att det fanns starka samband mellan doftkänslighet och känslighet för capsaicin. 6% av befolkningen hade doftkänslighet av sådan grad att detta påverkade personerna emotionellt och socialt kombinerat med en ökad känslighet för capsaicin. Vår slutsats blev att denna grupp representerade en egen sjukdomstyp som fick namnet sensorisk hyperreaktivitet i luftvägarna (SHR).

I studie IV undersöktes sambanden mellan SHR och astma. Dessutom undersöktes betydelsen av rökning och benägenhet för oro och ångest för förekomsten av SHR. Astma och SHR tycks vara helt skilda sjukdomar och rökning tycks inte öka risken för SHR. Oro, ångest och depression är vanligt vid alla kroniska sjukdomar, även vid luftvägssjukdomar, men SHR tycks inte vara speciellt kopplat till psykisk ohälsa vid jämförelse med allergi- och astmapatienter.

Slutsatsen blir att doftkänslighet är vanligt i den svenska befolkningen. En grupp av dessa personer med påvisbar ökad känslighet i luftvägar, mätbar med capsaicintest, kan avgränsas och deras sjukdom kan definieras som SHR. Denna sjukdom tycks inte ha något samband med astma och inte heller med förändrat luktsinne eller rökning. Luftvägssjukdomar medför ofta en psykisk påfrestning och med hänsyn till detta kan inte något speciellt samband mellan SHR och psykisk ohälsa påvisas.

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