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Odor-related Chronic Somatic Symptoms Are Associated with Self-Reported Asthma and Hay Fever: The Hordaland Health Study

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ABSTRACT

The aetiology behind odor-related chronic somatic symptoms (O-RCSS) is unknown, although both immunological and psychiatric causes have been suggested. The aim of this study was to investigate the occurrence of self-reported asthma and hay fever and psychiatric symptoms in individuals having O-RCSS compared to individuals with similar chronic somatic symptoms (CSS) which were not odors-related, and also compared to healthy controls.

Data from the Hordaland Health Study were used. 13,799 individuals, 40-45 years, answered a questionnaire including 16 questions related to somatic symptoms. They also indicated if the symptoms were odor-related, and answered questions about asthma and hay fever. Anxiety and depression were measured with the Hospital Anxiety and Depression Scale.

38 (0.6%) men and 106 (1.4%) women had O-RCSS, whereas 88 (1.5%) men and 192 (2.5%) women had CSS. Adjusted logistic regression analyses showed increased odds of self-reported asthma in those with O-RCSS compared to those with CSS (males: 3.81, 1.06-13.8, females: 2.60, 1.05-6.93) and compared to male and female controls (3.56, 1.89-6.68 and 4.81, 1.92-12.1 respectively). Increased odds of self-reported hay fever were in addition seen in females with O-RCSS. There were no differences in psychiatric symptoms between individuals with O-RCSS and CSS, although individuals in both groups showed increased odds compared to male and female controls.

Increased occurrence of self-reported asthma was exclusively found among male and females with O-RCSS, compared to CSS and controls. Increased occurrence of psychiatric symptoms was seen both in individuals with O-RCSS and CSS.

Keywords: Anxiety; Asthma; Chemical sensitivity; Hay fever; Somatization

INTRODUCTION

We are daily surrounded by different odors. Some odors are attractive while others are disgusting. The ability to smell is important and useful, for instance to avoid dangerous situations as fire and poison, but also to enjoy food. However, some individuals develop severe chronic somatic symptoms in multiple organ systems which they relate to exposure to specific

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common odors, a condition often referred to as multiple chemical sensitivity (MCS).[1] This condition refers to recurrent, self-reported severe symptoms from multiple organ systems. The symptoms relate to exposure to a wide range of chemically unrelated substances at levels normally considered non-toxic. Frequently reported symptom-eliciting agents include perfume, exhausts, cleaning agents, freshly printed papers, and smoke.[1] In the scientific literature, also other terms of this condition have been used, such as idiopathic environmental intolerance, chemical intolerance, chemical sensitivity, and sensitivity-related intolerance.

Previous studies have shown different degrees of chemical sensitivity, ranging from mild chemical annoyance to disabling odor-related chronic somatic symptoms. Depending on the definitions, prevalences of chemical sensitivity between 9-33% have been reported in the general population.[2-4] For disabling odor-related chronic somatic symptoms prevalences have varied between 0.5% and 6.3%.[4-7] Women report higher prevalence of odor-related chronic somatic symptoms than men.[3,8]

The reasons why some individuals evolve odor-related chronic somatic symptoms is unknown. There is no conventional toxicological dose-response relationship between the odor concentration and the occurrence of the symptoms. The symptoms are almost exclusively non-specific, cannot be linked to any single organ or laboratory finding, and are also frequently reported in the general population.[9-11] The most frequently reported symptoms in individuals affected by odor exposure are gastrointestinal symptoms, headache, extreme fatigue, muscle and joint pain, upper airway symptoms, irritability and cognitive deficits.[8]

In a review article, Genuis[12] showed that there is limited scientific literature on the pathogenic mechanisms involved in sensitivity-related illnesses. Several pathophysiological mechanisms have been proposed, such as sensitization, and symptom acquirement due to classical conditioning.[13-15] Double-blind placebo provocation studies with exposure to solvent concentrations below odor threshold found that individuals with MCS cannot differentiate active and sham exposures.[16] This finding suggests that psychological mechanisms are likely to be a causative part of the problem.[17] Increased levels of psychiatric symptoms, such as depression, anxiety, and somatization, are frequently reported.[18-20] On the other hand, increased reactivity in the skin and airways upon chemical exposure suggests that immunological factors might be involved.[21]

No previous studies have compared the occurrence of immunological and psychiatric factors in individuals with odor-related somatic symptoms with individuals having similar symptoms which are not odor-related. We wanted to explore if there was a difference in the relationship between immunological factors and odor-related symptoms compared to psychological factors and odor-related symptoms. In order to do so, we compared the occurrence of self-reported asthma, hay fever, anxiety and depression in individuals with and without odor-related chronic somatic symptoms and among healthy controls. Asthma and hay fever were chosen as these diseases may be caused by immunological mechanisms. Anxiety and depression represented psychological diseases.

MATERIALS AND METHODS

The Hordaland Health Study 1997–1999 (HUSK), Norway, was conducted as collaboration between the National Health Screening Service, the University of Bergen and local health services. The study protocol was approved by the Regional Committees for Medical and Health Research Ethics in Western Norway (REK-Vest) and by the Norwegian Data Inspectorate, and informed consent was collected for all participants. Health information used in this study was self-reported from the HUSK questionnaire.

Base Study Population

The base population included 29,395 individuals residing in Hordaland County, born between 1953 and 1957, aged between 40–45 years at the time. A total of 18,581 (8,598 men and 9,983 women) answered the basic questionnaire yielding a response rate of 63%. Only individuals who answered sixteen questions regarding somatic symptoms, and the single question whether the symptoms were odor-related, and questions about asthma, hay fever and psychiatric symptoms (see below) were included in the analyses, totally 13,799 individuals (6,007 men and 7,792 women).

Chronic Somatic Symptoms

Somatic symptoms in five organ systems were measured by sixteen questions, using a five-point scale (range: almost never, seldom, sometimes, often, and

almost always). Six questions were related to gastro-intestinal symptoms (abdominal pain, nausea, feeling bloated or full of gas, bad taste in mouth, or excessively coated tongue, complaints of vomiting or regurgitation of food, and complaint of frequent and loose motions of discharge off fluids from anus), two questions were related to cardiovascular symptoms (breathlessness without exertion, and chest pains), two questions were related to genito-urinary symptoms (dysuria or complaints of frequency of micturition, and unpleasant sensations in or around the genitals), and three questions were related to skin and pain symptoms (complaints of blotchiness or discoloration of the skin, pain in the limbs, extremities or joints, and unpleasant numbness or tingling sensation). These 13 questions were obtained from the ICD-10 symptom criteria of somatization disorder (ICD-10, F45.0). In addition three questions were related to CNS symptoms (headache, dizziness, and marked tiredness).

Subsequently, the individuals answered one question regarding odor sensitivity: "do you experience any of the somatic symptoms above when you are exposed to smell of perfume, cooking smell, or exhaust or something similar?" (yes/no).

Participants were divided into three groups for the statistical analysis. Group 1 consisted of individuals with odor-related chronic somatic symptoms (O-RCSS) (i.e. individuals that almost always experienced somatic symptoms in at least two different organ systems, and confirmed that the symptoms were odor-related). Group 2 consisted of individuals with chronic somatic symptoms (CSS), which were not-odor-related (i.e. individual that almost always experienced somatic symptoms in at least two different organ systems, and confirmed that the symptoms were not odor-related). The third group (controls) were individuals not included in the two above mention groups (O-RCSS or CSS).

Asthma, Hay Fever, Anxiety and Depression

Information about former or present asthma (yes or no) and hay fever (yes or no) were obtained from the HUSK questionnaire. Psychiatric symptoms during the last week were measured with The Hospital Anxiety and Depression Scale (HADS).[22] HADS consists of 14 items, seven related to anxiety (HADS-A) and seven to depression (HADS-D). All items were scored on a four-point scale from 0 to 3. The scale has shown good psychometric properties[22,23] Symptoms of severe psychopathology were not included in the scale, which makes HADS more sensitive to milder psychopathology. Cut off scores of ≥ 8 were used to identify individuals with anxiety (HADS-A ≥ 8), depression (HADS-D ≥ 8) or comorbid anxiety and depression (both HADS-A and HADS-D ≥ 8)[24] HADS was used as a categorical variable with normal score as the reference.

Background Variables

Variables like educational level, occupation during the past twelve months, smoking habits, weekly physical activity, chronic diseases, house pet keeping (cat or dog), and use of medication were obtained from the HUSK questionnaire, and used as descriptive variables or as adjusting variables in the statistical analysis.

Education was categorized into five levels in the questionnaire, but regrouped into two levels in the statistical analyses; lower education (up to upper secondary school) and higher education (University and University College).

Occupation during the past twelve months was entered as free text by the participants. These occupations were assigned a four-digit numerical code in accordance with the International Standard Classification of Occupations (ISCO-88) by a trained person. In the statistical analyses, occupations were divided into two categories based on assumed levels of exposures to dust and gases: occupations with low exposure and occupations with high exposure. Two hundred and fifty-one occupations were assigned to low exposure and 53 to high exposure.

Smoking habits were sorted into two categories for the analyses: non-smokers (including both those who had never smoked and ex-smokers), and current smokers. Ex-smokers were defined as individuals who had stopped smoking more than one year before the survey, while current smokers had smoked daily for more than one year.

Individuals estimated weekly physical activity as follows: no physical activity, one hour a week, two hours a week and three or more hours a week.

Body mass index (BMI) (kg/m^2) was calculated based on height and weight obtained from the clinical examination. BMI was categorized into four levels using the World Health Organization's system: underweight (BMI< $18.5 kg/m^2$), normal weight (BMI $\leq$ 18.5-24.9 kg/m^2), overweight (BMI $\leq$ 25.0 – 29.9

kg/m^2) and obese (BMI > 30kg/m^2).

Individuals indicated the presence or absence (yes/no) of chronic diseases as multiple sclerosis, diabetes mellitus, angina pectoris, heart attacks and strokes. Individuals who at any time in their life have had one or more of the above-mentioned diagnoses/diseases were defined as an individual having a chronic disease.

Daily or almost daily use of medication during the last year was reported for each of the following: pain killers, sedatives, anti-depressants, allergy medications and asthma medication. In our analyses, we only distinguished between use and no use of such medication during the last year.

Statistical Analyses

The Statistical Products of Service Solution package (SPSS Statistics, version 19) was used for all statistical analyses. Crosstables and Pearson Chi-square tests were used to compare categorical variables in the three groups (O-RCSS, CSS and controls). Two series of logistic regression analyses were used to examine the association between having O-RCSS or CSS and asthma, hay fever, anxiety, depression and comorbid anxiety and depression. In the first model, individuals with O-RCSS and CSS where included with healthy controls as reference group. In the second model, individuals with O-RCSS were explored when individuals with CSS served as reference group. In both models we adjusted for educational level, occupational exposure to dust and gases, smoking habits, house pets, levels of physical activity, BMI and presence or absence of chronic diseases. All analyses were separated by sex. Since we have a narrow age range (40-45 years), we did not adjust for age. *P*-value of ≤0.05 was regarded as significant.

RESULTS

In the present study population, O-RCSS were found in 0.6% (n=38) of the men and in 1.4% (n=86) of the women, whereas CSS were seen in 1.5% (n=106) of the men and in 2.5% (n=192) of the women (Table 1).

Women with O-RCSS had lower education, were less physical active, had higher BMI, smoked more and had higher occurrence of chronic diseases than female controls (Table 1). In addition they used more painkillers, sleep medicine, sedatives, antidepressants, and allergy and asthma medicine than the controls. There were no significant differences in occupational exposure to dust and gases or in exposure from house pets between the two groups.

Women with O-RCSS had significantly higher education and BMI compared to women with CSS (Table 1). They used significantly more pain killers and allergy and asthma medicine, but there were no differences in use of sleep medicine, sedatives or antidepressants. There were no significant differences between the two groups in smoking habits, levels of physical activity, occurrence of chronic diseases, occupational exposure to dust and gases or in house hold pets.

Men with O-RCSS had significantly lower education, were less physical active, had occupations with more exposure of dust and gases and had more house pets than male controls (Table 1). They used more pain killers, sleep medicine, sedatives, antidepressants and asthma medicine, but there were no significant differences in use of allergy medicine compared to male controls. There were also no differences in smoking habits, BMI and in occurrence of chronic diseases between the two groups. Men with O-RCSS were significantly more physically active and reported more use of asthma medicine compared to men with CSS. There were no significant differences between the two groups in the other background variables.

Asthma, Hay Fever, Anxiety and Depression in Individuals with O-RCSS and CSS vs. Controls

Logistic regression analyses adjusted for educational level, occupational exposure, smoking habits, levels of physical activity, BMI and presence of chronic diseases showed that women with O-RCSS had significantly higher odds ratio (OR) of asthma, high fever, anxiety and comorbid anxiety and depression compared to female controls (Table 2).

Women with CSS had significantly higher OR of anxiety, depression and comorbid anxiety and depression compared to female controls (Table 2). A similar analysis for men showed significantly OR of asthma and comorbid anxiety and depression in those with O-RCSS compared to male controls. Men with CSS had significantly higher OR only of anxiety and comorbid anxiety and depression.

Table 1. Prevalence and significant levels in women and men with odor-related chronic somatic symptoms (O-RCSS), in women and men with chronic somatic symptoms which are not odor-related (CSS), and in healthy female and male controls.

	Women				Men			
	O-RCSS n=106	CSS n=192	Control n=7494	Sig.	O-RCSS n=38	CSS n=88	Control n=5881	Sig.
Chronic symptoms								
Gastrointestinal	57%	58%	3.1%	a, b) **	66%	66%	2.6%	a, b) **
Cardio-respiratory	8.5%	5.2%	0.1%	a, b) **	11%	21%	0.1%	a. b) **
Genitalia	4.7%	6.3%	0.1%	a, b) **	11%	16%	0.1%	a. b) **
Skin and muscular	85%	88%	7.4%	a, b) **	88%	76%	4.4%	a, b) **
CNS	69%	67%	1.7%	a, b) **	63%	61%	0.9%	a, b) **
Educational level								
Low	73%	76%	64%	a, c) **	79%	69%	62%	a) *
Occupational exposure								
High	2.9 %	3.1%	3.5%		34%	20%	18%	a) *
Smoking habits								
Yes	49%	48%	34%	a, b) **	45%	40%	34%	
House pets								
Having dog	23%	28%	18%	b) **	33%	18%	17%	a) **
Having cat	31%	27%	30%		29%	27%	26%	
Physical activity								
None	50%	55%	31%	a, b) **	38%	40%	24%	a, b) **,
1 hour weekly	27%	21%	28%		30%	33%	29%	c)*
2 hour	17%	17%	31%		2.7%	15%	29%	
3 or more hour	6.9%	7.0%	10%		30%	12%	18%	
Body mass index								
Underweight	1.9%	2.1%	1.4%	a) **, c) *	2.6%	0.0%	0.3%	
Normal	39%	56%	61%		29%	33%	39%	
Overweight	41%	26%	28%		58%	47%	48%	
Obese	19%	15%	9.8%		11%	21%	12%	
Chronic diseases								
Yes	7.7%	6.8%	2.1%	a, b) **	5.4%	8.2%	2.4%	b) **
Medication								
Painkillers	55%	48%	15%	a, b) **, c) *	42%	33%	10%	a, b) **
Sleep medicine	14%	18%	4.1%	a, b) **	14%	10%	2.2%	a, b) **
Sedatives	11%	14%	3.0%	a, b) **	11%	5.2%	2.0%	a) **, b) *
Antidepressants	23%	24%	6.1%	a, b) **	19%	12%	3.3%	a, b) **
Anti-allergy medicine	35%	18%	14%	a, c) **	17%	6.5%	11%	
Asthma medicine	23%	7.4%	5.1%	a, c) **	17%	5.2%	3.7%	a) **, c) *

[a)]Significant levels for comparisons between O-RCSS and controls [b)]Significant levels for comparisons between CSS and controls [c)]Significant levels for comparisons between O-RCSS and CSS., *p <.05, **p <.01

Asthma, Hay Fever, Anxiety and Depression in Individuals with O-RCSS vs. CSS

Logistic regression analyses adjusted for potential covariates indicated that women with O-RCSS had significantly higher OR of asthma and high fever compared to women with CSS (Table 3). There were no significant differences in levels of anxiety, depression and comorbid anxiety and depression between the two groups.

Table 2. Odds ratio (OR) and 95 % CI of self-reported asthma, hay fever, anxiety, depression and comorbidity of anxiety and depression in women and men with odor-related chronic somatic symptoms (O-RCSS) and chronic somatic symptoms (CSS) after adjusting for possible confounders. Healthy controls served as reference.

Women	O-RCSS (n=106)	OR (95%CI)	CSS (n=192)	OR (95%CI)	Control (n=7494)
Asthma	22%	**3.56 (1.89-6.68)**	7.9%	1.51 (0.80-2.86)	6.4%
Hay fever	33%	**2.72 (1.58-4.68)**	17%	0.94 (0.55-1.61)	15%
Anxiety	26%	**3.08 (1.79-5.29)**	26%	**2.85 (1.91-4.27)**	14%
Depression	3.8%	1.08 (0.26-4.49)	5.8%	**2.48 (1.17-5.26)**	2.4%
Comorbidity	34%	**5.89 (3.27-10.6)**	27%	**4.99 (3.17-7.86)**	5.5%
Men	**(n=38)**	**OR (95%CI)**	**(n=88)**	**OR (95%CI)**	**(n=5881)**
Asthma	24%	**4.81 (1.92-12.1)**	10%	1.77 (0.75-4.14)	5.3%
Hay fever	29%	1.89 (0.80-4.50)	12%	0.71 (0.34-1.50)	16%
Anxiety	13%	2.05 (0.77-5.44)	18%	**2.26 (1.22-4.18)**	9.4%
Depression	7.9%	1.33 (0.31-5.73)	11%	2.05 (0.92-4.57)	4.8%
Comorbidity	37%	**7.18 (3.17-16.3)**	29%	**5.05 (2.85-8.94)**	6.4%

Table 3. Odds ratio (OR) and 95 % CI of self-reported asthma, hay fever, anxiety, depression and comorbidity of anxiety and depression in women and men with odor-related chronic somatic symptoms (O-RCSS) after adjusting for possible confounders. Men and women with similar chronic somatic symptoms that are not odor-related (CSS) served as reference.

	Women OR (95% CI)	Men OR (95% CI)
Asthma	**2.60 (1.05-6.93)**	**3.81 (1.06-13.8**)
Hay fever	**3.16 (1.44-6.92)**	3.47 (0.95-12.6)
Anxiety	0.94 (0.47-1.87)	0.69 (0.20-2.38)
Depression	0.34 (0.05-2.14)	0.54 (0.09-3.18)
Comorbidity	1.25 (0.59-2.63)	1.54 (0.53-4.42)

Logistic regression analyses adjusted for potential covariates showed that men with O-RCSS had significantly higher OR of asthma compared to men with CSS (Table 3). There were no significant differences in hay fever, levels of anxiety, depression and comorbid anxiety and depression between the two groups.

DISCUSSION

Our results showed an association between self-reported asthma and O-RSCC, as well as between hay fever and O-RSCC. Men and women with O-RCSS had significantly higher prevalence of self-reported asthma compared with men and women with CSS, and compared with male and female controls.

In addition women with O-RCSS had a higher prevalence of self-reported hay fever. There was no significant difference in the levels of anxiety and depression between individuals with O-RCSS and CSS, although the levels in both groups were higher than in controls.

Our results may support the hypothesis that immunological factors are involved in the pathogenesis of odor-related chronic somatic symptoms. Asthma and hay fever are of course only a kind of proxy for immunological diseases in the present study, but the relationship between these diseases and O-RSCC is clear in the present analyses. Immunological changes have been suggested by numerous authors as the pathogenesis of odor-related chronic somatic symptoms. De Luca and colleagues suggested odor-related somatic symptoms to be due to immunological and biochemical disturbances [25], and to chronic oxidative stress [26]. Furthermore a dose-dependent non-immunological IgE mediated release of histamine from peripheral blood basophils has been shown after perfume exposure.[27] It has also been suggested that chemical sensitivity might result from bonding of low molecular weight chemical compounds to chemoreceptors on sensory nerve C-fibres which leads to release of inflammatory mediators.[28]

Our findings are in line with previous studies in general populations that have reported associations between odor-related somatic symptoms and asthma.A telephone survey in North Carolina including 1027

individuals showed that simultaneous allergy and chemical sensitivity were reported by 16.9% of the population.[4] Similarly, Kreutzer and colleagues[6] showed an association between asthma and allergic reactions and chemical intolerance in a population based survey from California including 4046 individuals. Furthermore, population study from US, including 1058 individuals, showed an association between asthma and chemical hypersensitivity.[29] Caress and Steinemann[30] found that among those diagnosed with MCS, 42% also reported to have been diagnosed with asthma.

In another study, 20.3% of patients from two primary care clinics met the criteria for chemical intolerance according to the Quick Environmental Exposure and Sensitivity Inventory questionnaire. Individuals with chemically intolerance reported significantly higher rates of comorbid allergies and they more often met criteria for possible major depressive disorder, panic disorder, generalized anxiety disorder, and alcohol abuse disorder, as well as somatization disorder.[31]

Our results also showed that there were no significant differences in anxiety and depression symptoms between individuals with CSS and O-RCSS, indicating that psychiatric symptoms were not only present for those with O-RCSS. However, compared to male and female controls, higher prevalences of anxiety and depression were reported in both groups. These findings are in accordance with previous studies showing that individuals with odor-related somatic symptoms had higher level of anxiety and depression compared to controls.[20,31-33] In a recent PET study, Hillert and colleagues[34] reported evidence that harm avoidance is an important part of the aetiology of MCS. Classical conditioning,[15] expectancy of severe somatic symptoms related to odor-exposure,[35] and panic disorder in relation to odor-exposure[36] have been suggested as possible explanations of odor-related chronic somatic symptoms.

The present study indicates no relationship between O-RCC and anxiety or depression. This is in line with findings of Caress and colleagues[37] who showed that only 1.4% of individuals with odor-related symptoms had a history of prior emotional problems before odor-related somatic symptoms evolved. However, Caress and colleagues also showed that 38% developed emotional problems after appearance of physical symptoms. This is not supported by our present study. However, our methods were different and we have no knowledge about when the different symptoms started. Also, another case-control study has suggested that individuals with chemical intolerance have a history of physical or psychiatric/psychological problems prior to their symptoms.[38]

This study has several limitations. The cross-sectional design makes it difficult to establish any causality between asthma, hay fever and O-RCSS. However, results from the regression analyses do support an association between these factors. The present study are based upon self-reports only, and has no objective measures of asthma or hay fever. However, previous studies have suggested an association between self-reports of these diagnoses and objective measures of atopy, such as high levels of Immunoglobulin E.[39] Several other questions and test could have been added to improve the present study. However, one of the strengths was that the questions were asked in the frame of a larger study with main focus on other disorders and complaints than O-RCSS. This may have increased the validity of our results.

Our results showed that individuals with O-RCSS and CSS had lower scores than male and female controls on indicators on health, lifestyle and socioeconomic status. This is also seen in other studies.[31] In this study we controlled for such factors by appropriate statistical methods.

In conclusion, odor-related chronic somatic symptoms in multiple organ systems are associated with self-reported asthma, hay fever, anxiety and depression. Chronic somatic symptoms which are not odor-related, are associated with self-reported anxiety and depression, but not with self-reported asthma and hay fever. The results support that immunological factors may be involved in the pathogenesis of odor-related somatic symptoms, although we cannot exclude that also psychiatric factors contribute. Future studies on this topic should be performed, including both questionnaire data and objective immunological measures.

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