Olfaction in COPD*

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Abstract

Background: Olfaction is poorly characterized in COPD. To test the hypothesis that olfaction is reduced in COPD, we assessed olfaction with the "Sniffin' Sticks" test and a questionnaire addressing olfaction in COPD and a corresponding control group in respect to age and sex. We also explored whether there is an association between COPD, chronic rhinosinusitis without nasal polyps (CRSsNP), and other predefined covariates with olfactory function.

Methodology: Olfactory function was assessed by the score for threshold (T), discrimination (D) and identification (I), and the composite TDI score in the "Sniffin' Sticks" test and by self-reported evaluation of impaired olfaction and of "decreased sense of smell and taste" in the 22-item Sino-Nasal Outcome Test (SNOT-22) in 90 COPD patients and 93 controls. A clinical interview and ENT-examination with nasal endoscopy, skin prick test and spirometry with reversibility were performed.

Results: The TDI, D and I scores were significantly lower in the COPD group than in the control group. The T score was not significantly different between the two groups. Hyposmia and anosmia were present in up to 79% of patients with COPD. The prevalence of self-reported impaired olfactory function and for "decreased sense of smell and taste" - was more than two-fold greater in the COPD than in the control group. COPD, higher age, male sex and allergy were associated with a lower TDI score, while CRSsNP was not associated with the TDI score.

Conclusions: COPD is associated with olfactory dysfunction and the underlying mechanisms for this dysfunction should be elucidated.

Key words: olfaction disorders, respiratory system, rhinitis, sinusitis, smell

Introduction

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality in modern society, and the burden of COPD is increasing globally [(1)]. Tobacco smoking is the primary cause, and other causes could be occupational exposure to smog and gases, household exposure to biomass smoke in developing countries and alpha1-antitrypsin deficiency. The lung function impairment in COPD patients is due to small airways constriction and parenchymal destruction [(2)].

The concept of united airway diseases is based on the reciprocal association of disease processes in the upper and lower airways and considers the upper and lower airways as one entity [(3)]. Associations of sinonasal symptoms and chronic rhinosinusitis with (CRSwNP) and without nasal polyps (CRSsNP) with COPD have been reported in observational [(4, 5)] and epidemiological studies [(6)], and nasal symptoms are increased progressively over time [(7)].

The nose is the sensory organ for olfaction, and olfactory dysfunction is prevalent in smokers, chronic rhinosinusitis (CRS), and neurodegenerative diseases. Although tobacco smoking is

associated with COPD, there are, to date, few studies of olfactory dysfunction in COPD. In one study, the odds ratio for self-reported anosmia increases by 1.19 % per year in these patients [7]. Of the other two studies [8, 9], different psychophysical tests are used to assess olfaction. The University of Pennsylvania Smell Identification Test (UPSIT) [10], which was used in the Dewan et al. study [8] limits olfactory assessment to odour identification. On the other hand, the Caglar et al. study [9] used the "Sniffin' Sticks" test, which also allows the assessment of odour threshold and discrimination, and the composite score of threshold, discrimination, and identification (TDI score) is a better assessment of olfactory function [11]. However, both studies lack self-reported assessment of olfaction and investigated groups that were predominantly male and small, with 40 subjects in the COPD group and between 20 to 33 subjects in the control group.

To better our understanding of olfactory function in COPD and for counselling this large group of patients, further studies with the use of validated tools in larger study groups are needed. We have recently reported a prevalence of 51% of CRSsNP in COPD in an observational study of a larger sample of COPD and control subjects [4]. To test the hypothesis that olfaction is reduced in COPD, we assessed olfaction with the "Sniffin' Sticks" test and a self-administered questionnaire addressing olfaction in COPD and a corresponding control group in respect to age and sex. We also explored whether there is an association between COPD, CRSsNP, and other predefined covariates with olfactory function.

Materials and methods

Study design and setting

This cross-sectional study was conducted between February 2016 and December 2017. The study sample has been previously described [4]. All subjects gave written informed consent, and all examinations and questionnaires were completed on the same day. The study was approved by the Regional Committee for Medical and Health Research Ethics, Central Norway, REC (reference number 2015/2017), and investigations were performed in accordance with the principles of the Declaration of Helsinki/ Hong Kong.

Subjects

COPD patients

Ninety COPD patients were recruited from the hospital respiratory outpatient and physical therapy clinics, general practitioner offices and a private pulmonology practice.

Inclusion criteria:

- Age 40-80 years.
- Diagnosis of COPD confirmed by a post-bronchodilator forced expiratory volume in 1 s (FEV_1) to forced vital capacity (FVC) ratio of <0.7 and a negative bronchodilator reversibility test.

Controls

Ninety-three controls were recruited locally from nearby businesses, multiple retirement associations and via the hospital's social media page.

Inclusion criteria:

- Age 40-80 years.
- No known disease of the upper and lower airways.

Exclusion criteria for both groups:

- Asthma (including Asthma on COPD overlap (ACO)).
- Pregnancy or breast feeding.
- Upper- and lower respiratory tract infection within the previous two weeks.
- Exacerbation within previous six weeks.
- Previous sinonasal surgery or nasal polyposis.
- Cystic fibrosis.
- Parkinson disease or Alzheimer disease.
- Ongoing radio-chemotherapy or use of long-term oxygen therapy.

All subjects were instructed to discontinue the use of systemic corticosteroids and antihistamines 4 days and nasal decongestants 12 hours prior to the inclusion visit. Nasal corticosteroids were continued. COPD patients were instructed not to take their morning inhaled medication because we wanted to determine whether there was any evidence of reversible airflow obstruction and in accordance with the standardized procedure for spirometry with reversibility testing [12].

Variables

Questionnaires on olfactory symptoms, subjective evaluation of olfaction, symptoms of allergy affecting the airways and smoking habits were self-administered. Subjects were categorized into current, former and never smokers. Pack-year exposure and body mass index (BMI) were calculated.

All subjects underwent an interview and a clinical ENT-examination with nasal endoscopy (2.7mm, 0° True View II endoscope, Olympus, Japan) of the olfactory cleft was performed by one of three otolaryngologists committed to the study (WMT, MRØ, SBD) to exclude anatomical abnormalities, tumours, nasal polyps and other pathologies that may affect olfaction. The endoscopic appearance of the nasal cavity was graded using the modified Lund-Kennedy endoscopy score (MLK) [13] based on oedema (0: absent; 1: mild; 2: severe), and discharge (0: none; 1: clear; 2: thick and purulent).

Flow volume spirometry (Medikro Pro spirometer, Kuopio, Finland) with reversibility testing [12], using reference values from Crapo et al. [14] was performed to confirm the presence of irreversible airflow obstruction. The severity of airflow obstruction was graded according to the GOLD 2014 criteria [2].

CRS symptoms were detected from the responses to the

SNOT-22 questionnaire and were defined as (a) nasal blockage/obstruction/congestion, (b) nasal discharge (anterior/posterior nasal drip), (c) facial pain/pressure and (d) reduction or loss of smell. The first two symptoms were defined as cardinal symptoms [6]. The EPOS 2020 criteria for CRS requires the presence of at least two of the four symptoms, of which one symptom is a cardinal symptom and a positive nasal endoscopy [15]. A positive nasal endoscopy was defined as unilateral or bilateral presence of oedema and/or mucopurulent discharge in the middle meatus [15].

Subjects were asked the following specific questions about allergy: "Have you ever had hay fever or nasal allergies?", "Have you had hay fever or nasal allergies during the last 12 months", "Do you have symptoms from the nose or eyes when exposed for pets, pollen or house dust mite?" and "Which of the following allergens do you think you are allergic to?" with the possibility to answer yes or no to birch, grass, mugwort, house dust mite, horse, dog and cat. A skin prick test (SPT) with an allergen panel consisting of birch, grass and mugwort pollen, cladosporium, house dust mite (*Dermatophagoides pteronyssinus*), and horse, dog and cat epithelia, together with positive and negative controls (Soluprick SQ, ALK-Abello, Horsholm, Denmark) was performed. A diagnosis of allergic rhinitis was based on an affirmative answer to all the above questions and a positive SPT to the allergen(s) specified by the subject [16].

Olfactory function with "Sniffin' Sticks"

Odour threshold (T), odour discrimination (D) and odour identification (I) were sequentially assessed with the extended "Sniffin' Sticks" test-kit (Burghart Messtechnik, Wedel, Germany) [17-19] and in accordance with the instructions in the manufacturer's test manual. Pens from each pen triplet were presented to both nostrils and in a randomized order that was concealed from the subject.

The threshold for n-butanol was determined by a single staircase method of presentation of triplets of pens containing ascending concentrations of n-butanol from triplet 16 to triplet 1. The subject was tasked to identify the n-butanol containing pen in each triplet. At the turning point, defined as two consecutive correct responses, the staircase was reversed, with presentation of descending concentrations until the first error. This again triggered a reversal of the staircase, and the test was stopped after a total of 7 reversals. The T score is the mean value of the last four reversals.

Discrimination was assessed by presentation of 16 triplets of pens. For each triplet, the subject was tasked with identifying the pen that had a different smell than the other two pens. The D score is the number of times that the different smell was correctly identified.

Identification was assessed by presenting pens containing one of the following 16 odours: orange, peppermint, turpentine, clove, leather, banana, garlic, rose, fish, lemon, coffee, cinnamon, liquorice, apple, pineapple, and aniseed. The subject was tasked to identify the item that best describes the presented odour from a list of four items. The I score is the number of odours that were correctly identified.

Olfactory function was classified by the TDI score, which is the summation of the T, D, and I score. A TDI score ≤16 indicates anosmia, a score between 16.25 and 30.5 is hyposmia and a score ≥30.75 is normosmia [20].

Subjective evaluation of olfaction

Subjects were asked to answer questions whether their olfaction was "normal" or "reduced". A question on "decreased sense of smell and taste " in the 22-item Sino-Nasal Outcome Test (SNOT-22) (21) was answered on a Likert scale with a response range from 0-5, where 0 equals no problem and 5 equals problem as bad as it could be. The response was dichotomized by defining a response of 0-1 as "no decreased sense of smell and taste" and of 2-5 as "decreased sense of smell and taste" (6).

The presence of impaired olfaction was assessed on a 100 mm Visual Analogue Scale (VAS), with 0 mm as not present and 100 mm as troublesome as possible.

Moreover, subjects were asked questions about phantosmia ("Do you smell odours in absence of an apparent source?") and parosmia ("Do you smell odours differently compared to previous experiences?") based on a binary outcome of "yes" and "no".

Sample size

A sample size analysis showed that 63 subjects were needed in each group to detect a difference of 2.5 in mean TDI between the groups with a significance level of 0.05 and a power of 80%.

Statistical analysis

For the statistical analysis, the IBM SPSS 25.0 was used. Continuous variables are presented as means and standard deviations (SD). Categorical variables are presented as frequencies and percentages (%). For group comparisons, independent t-test was used for normally distributed data and the Mann–Whitney U test was used for non-normally distributed data, while categorical data were analysed using Chi-Square tests or Fisher's Exact Test when appropriate. After checking that the assumption of normality was fulfilled, multiple linear regression analysis was undertaken to investigate variables associated with TDI and the results are presented with β and 95% confidence intervals (CI). A difference was considered significant at a p value of < 0.05.

Results

Characteristics of the study population

Ninety and 93 subjects were enrolled in the COPD and control groups, respectively. Age, sex, smoking status, BMI, CRSsNP, allergic rhinitis and nasal corticosteroid use, together with lung

Table 1. Subject characteristics.

	COPD		Control		P value
N	90		93		
Age years	66.2	(8.7)	63.7	(8.7)	0.051
Female	41	(45.6)	42	(45.2)	0.96
Smoking information					
Current smokers	17	(18.9)	7	(7.5)	<0.001
Former smokers	68	(75.6)	47	(50.5)	
Non-smokers	5	(5.5)	39	(42)	
Pack-years#	28.6	(20.9)	6.6	(10.8)	<0.001
BMI	27.0	(5.4)	27.3	(4.7)	0.7
CRSsNP	46	(51.1)	15	(16.1)	<0.001
MLK	2.8	(2.0)	1.4	(1.8)	<0.01
Allergic rhinitis	5	(5.6)	14	(15.1)	0.035
Nasal corticosteroids	4	(4.4)	4	(4.3)	1.0
Lung function*					
FEV_1 (l)	1.6	(0.7)	3.0	(0.9)	< 0.001
FEV_1 (% predicted)	53.1	(18.7)	94.6	(12.2)	< 0.001
FVC (l)	3.0	(1.0)	3.7	(1.0)	< 0.001
FVC (% predicted)	75.8	(18.0)	93.8	(13.0)	< 0.001
FEV_1/FVC	0.53	(0.12)	0.78	(0.05)	< 0.001

Data presented as n (%) or mean (SD) unless otherwise stated. P-values refer to data comparison between COPD and controls. #missing data in 4 controls and 3 COPD; *pre-bronchodilator values in 2 controls and 1 COPD. Otherwise, pulmonary function parameters are based on post-bronchodilator measurements. COPD: chronic obstructive pulmonary disease; BMI: body mass index; CRSsNP: chronic rhinosinusitis without nasal polyps; MLK: modified Lund Kennedy endoscopy score; FEV_1: forced expiratory volume in 1s; FVC: forced vital capacity.

function are summarized in Table 1. Current smokers and CRSsNP were two- and three-fold greater in the COPD group and allergic rhinitis was three-fold greater in the control group.
The MLK assessing oedema and discharge was significantly higher in COPD than in the control group [mean (SD) 2.8 (2.0) vs 1.4 (1.8), p<0.01].
Of the COPD patients, airflow limitation was categorized as GOLD 1 in 7.8 % (n=7), GOLD 2 in 44.4 % (n=40), GOLD 3 in 36.7 % (n= 33) and GOLD 4 in 11.1 % (n=10).

Primary outcome data and main results

The TDI score was significantly lower in COPD than in the control group [mean (SD) 25.7 (5.7) vs 28.1 (5.6), p=0.005]. The T score was not significantly different between the COPD and control groups [mean (SD) 4.7 (2.0) vs 5.0 (2.3), p=0.31]; D and I scores were significantly lower in COPD than in the control group [mean (SD) 10.2 (2.6) vs 11.3 (2.5), p=0.006 and 10.8 (2.7) vs 11.8 (2.4), p=0.006], respectively (Figure 1).
On subgroup analysis, the TDI, T, D and I scores were significantly lower in former smokers in the COPD than in the control group. In the absence of allergic rhinitis, the TDI, D and I scores were significantly lower in the COPD than in the control group; the T score was not significantly different between the groups (Table 2).
In the COPD group, the TDI, T, D and I scores were not significantly different between subjects with and without CRSsNP, respectively; TDI [mean (SD) 25.9 (5.7) vs 26.0 (5.9), p=0.5], T [mean (SD) 4.8 (2.1) vs 4.6 (1.9), p=0.7], D [mean (SD) 10.2 (2.5) vs 10.3 (2.7), p=0.7], and I [mean (SD) 10.5 (2.5) vs 11.2 (2.8) p=0.7].
In the adjusted linear regression analysis (Table 3), CRSsNP was not associated with a lower TDI, T, D, or I score. COPD, higher age, male sex and allergy were associated with a lower TDI score. These 5 variables accounted for 21% of the variance for the TDI score. Of these variables, COPD was not associated with a lower T score and was associated with a lower D and I score. Higher age was associated with a lower T, D and I score. Male sex and allergy were associated with a lower T and I score and were not associated with a lower D score.
Normosmia was almost two- fold more prevalent in the control group than in the COPD group. Olfactory dysfunction with either anosmia or hyposmia was present in 79% and 61% in the COPD and control groups (p=0.01), respectively (Figure 2a).

Secondary outcome data

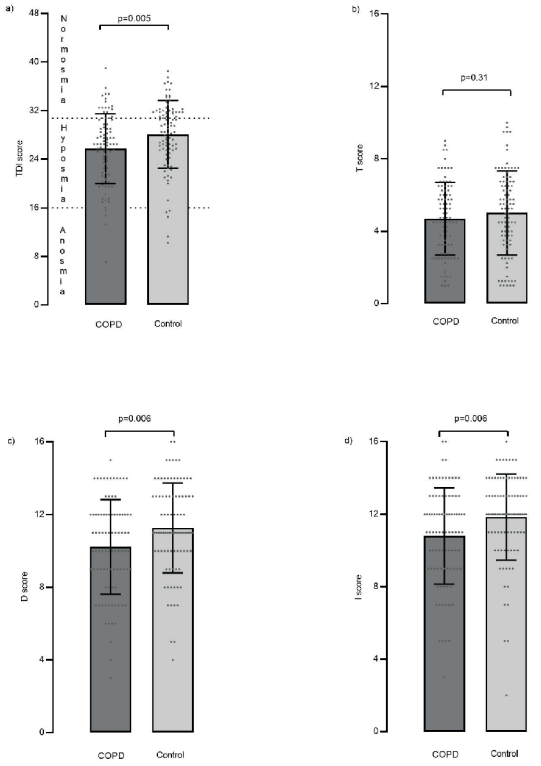

Figure 1. TDI (panel a), T (panel b), D (panel c) and I (panel d) scores in COPD and control groups. Data presented as means and SD and individual values. TDI= sum of the T, D, and I scores, T= threshold, D= discrimination, I= identification. COPD: chronic obstructive pulmonary disease.

The prevalence was more than two-fold greater in the COPD than in the control group for self-reported impaired olfactory function (30 % vs 14%, p=0.02) and for decreased sense of smell and taste by SNOT-22 (36.7% vs 15.1%, p<0.01; Figure 2b).
In the COPD group, the TDI score was significantly lower in subjects reporting a decrease than in those reporting no decrease in sense of smell and taste by SNOT-22 [mean (SD) 23.8 (6.9) vs 26.9 (4.6), p=0.03]. In the control group, there was no significant difference in the TDI score in subjects with or without a decrease in sense of smell and taste [mean (SD) 27.7 (5.9) vs 28.2 (5.6), p=0.7]. For both groups, the mean scores of the subjects who reported no decrease in smell and taste were within the range for hyposmia (Figure 3).
Of those who reported no decrease in smell and taste, the TDI score was in the normosmia range in 23% and 39% in the COPD and control group, respectively (p=0.04). For those who reported a decrease in smell and taste, the TDI score was in the normosmia range in 18% and 35% in the COPD and control group, respectively (p=0.2).
The VAS score of impaired olfaction was significantly greater in the COPD group than in the control group [mean (SD) 16.2 (25.4) vs 6.9 (15.4) p=0.02].
The prevalence of parosmia and phantosmia was not significantly different in the COPD and control groups (11.1% vs 10.8 %, p = 0.96 and 22.2% vs 20.9%, p = 0.78), respectively.

Discussion

Key results

In this study, we have demonstrated that olfactory function assessed by the TDI score from the "Sniffin' Sticks" test was poorer in the COPD than in the control group. D and I scores were significantly lower in the COPD group, while there was no significant difference in the T score between the two groups. In regression analysis, COPD was associated with TDI, D and I scores, but was not associated with the T score. Higher age was associated with lower TDI and all 3 component scores, and male sex and allergy were associated with lower TDI and T scores. However, CRSsNP was not associated with TDI or any of the 3 component scores. Olfactory dysfunction was underreported in both groups and many subjects had TDI scores in the range for hyposmia. Underreporting was more frequent in the control than in the COPD group.

Interpretation

Our finding of reduced olfactory function in COPD extends the finding of reduced identification using the UPSIT test in the study by Dewan et al. [8] and complements those of reduced TDI, D and I scores to "Sniffin' Sticks" in the Caglar et al. [9] study.

Table 2. Sub-group analysis of olfactory scores in former smokers and without allergic rhinitis in COPD and control groups.

Olfactory score	Former smokers			Without allergic rhinitis		
	COPD (n=68)	Control (n=47)	P value	COPD (n=85)	Control (n=79)	P value
TDI	25.3 (6.1)	28.9 (6.0)	<0.01	25.9 (5.8)	28.5 (5.3)	0.003
T	4.5 (1.9)	5.4 (2.3)	0.04	4.7 (1.9)	5.2 (2.2)	0.2
D	10.2 (2.7)	11.5 (2.5)	<0.01	10.2 (2.6)	11.3 (2.5)	0.005
I	10.6 (2.7)	12.1 (2.6)	<0.01	10.9 (2.7	12.0 (2.2)	0.006

Data presented as mean (SD). Abbreviations: TDI= sum of the T, D, and I scores; T= threshold; D= discrimination; I= identification; COPD: chronic obstructive pulmonary disease.

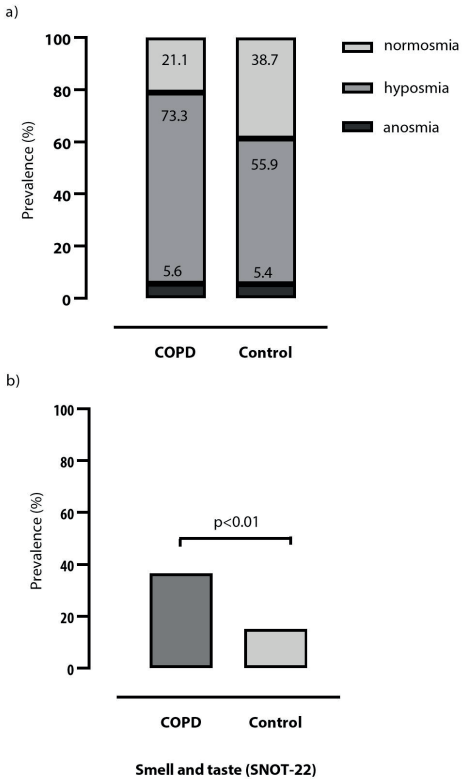

Figure 2. Prevalence of anosmia, hyposmia and normosmia (panel a) and of self-reported decreased sense of smell and taste in SNOT-22 (panel b) in COPD and control groups. COPD: chronic obstructive pulmonary disease; SNOT-22: Sino-Nasal Outcome-Test 22.

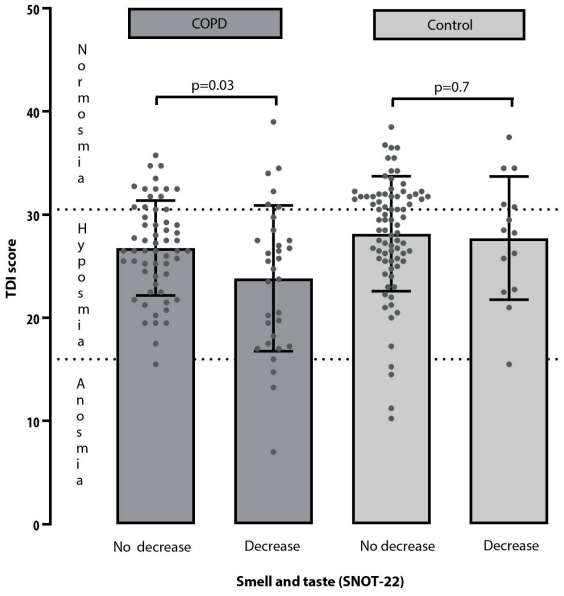

Figure 3. TDI scores in COPD and control groups categorized by self-reported "No decrease" and "Decrease" smell and taste in SNOT-22. Data presented as mean (SD) and individual values. A TDI score ≤16 indicates anosmia, a score between 16.25 and 30,5 is hyposmia and a score ≥30.75 is normosmia. COPD: chronic obstructive pulmonary disease; TDI= sum of the T, D and I scores; SNOT-22: Sino-Nasal Outcome-Test 22.

However, the present study diverges from the latter study with respect to the T score. The T score in that study was significantly lower in the COPD compared to the control group. In the present study, there was no significant difference in this score between the two groups. A possible explanation could be that the T-score in the control group in our study is <6, which is defined as olfactory dysfunction by Kohli et al. [24]. Further, regression analysis showed that male sex was associated with a lower T score than female sex. Compared to our study, the T score in the COPD group in the Caglar et al. [9] study is lower than that in the COPD group in our study. This may be due to the greater preponderance of males in that study. The combination of these factors may explain why there is no significant difference in the T-score in the two groups in the present study.

It is possible that the lower D and I scores in COPD may be due to depression and cognitive impairment. The suprathreshold tests of D and I are suggested to preferentially assess central or cognitive causes of olfactory loss [25]. Olfactory performance, with decreased scores for D and I, has been reported to be reduced in patients with depression [26]. Moreover, cognitive impairment is also associated with decline of olfactory function [27]. Although we did not assess depression and cognitive impairment, the estimated prevalence of depression in COPD is 80% [28] and patients with severe COPD are at greater risk for developing cognitive impairment [29].

In the present study, the prevalence of CRSsNP was 51% in COPD and 16% in controls, and CRSsNP was not associated with a lower TDI, T, D or I score in the regression analysis. The prevalence of olfactory dysfunction is sub-group dependent, being higher in CRSwNP than in CRS mixed populations [30]. In a recent meta-analysis [24] nasal polyps, inflammatory changes apparent on CT scans and higher age were the factors that were most frequently associated with olfactory dysfunction. However, CRSsNP was not reported as a distinct subgroup in the studies that were included in the meta-analysis. As CRSwNP were excluded in our study, it is possible that an association with the "Sniffin' Sticks" could be present in a larger study population and with CRSwNP included.

Our findings that being male, older age and having allergy was associated with a lower TDI score are supported by other studies. The association of the first 2 variables with poorer performance in olfactory tests has been reported by other studies [20, 31], and allergy is known to affect the olfactory function likely due to a mechanical and inflammatory component [32]. In the present study 5.6% of COPD patients and 15.1% of controls had seasonal allergic rhinitis examined outside of the allergy season. When these individuals were excluded from our subanalysis, the TDI, D and I were still significantly different between COPD

Table 3. Adjusted linear regression for psychophysical scores of olfactory function.

Variable	Estimate of β	95% CI	P value
TDI			
COPD	-2.3	-3.9 to -0.6	<0.01
Age [years]	-0.2	-0.3 to -0.2	<0.01
Sex [male]	-1.8	-3.4 to -0.3	0.02
Allergy	-2.8	-5.4 to -0.4	0.03
CRSsNP	0.7	-1.1 to 2.4	0.4
T			
COPD	-0.4	-1.1 to 0.3	0.2
Age [years]	-0.6	-0.1 to -0.03	<0.01
Sex [male]	-0.8	-1.3 to -0.2	0.01
Allergy	-1.1	-2.2 to -0.1	0.03
CRSsNP	0.3	-0.4 to 1.1	0.4
D			
COPD	-0.9	-1.7 to -0.1	0.02
Age [years]	-0.1	-0.1 to -0.05	<0.01
Sex [male]	-0.3	-0.5 to 0.9	0.5
Allergy	-0.5	-1.7 to 0.7	0.4
CRSsNP	0.13	-0.7 to 1.0	0.7
I			
COPD	-2.0	-3.6 to -0.5	0.01
Age [years]	-0.2	-0.1 to -0.05	<0.01
Sex [male]	-1.9	-3.4 to -0.4	0.02
Allergy	-2.8	-2.3 to -0.8	0.04
CRSsNP	0.2	-0.6 to 1.0	0.6

Number of subjects in analysis=183; Adjusted R2 for TDI, T, D and I was 21%, 11%, 11% and 16%, respectively. TDI= sum of the T, D and I scores; T= threshold; D= discrimination; I= identification; β=unstandardized coefficient; CI=confidence interval; COPD: chronic obstructive pulmonary disease; CRSsNP: chronic rhinosinusitis without nasal polyps.

and controls. Despite this, both allergy and olfaction should be addressed in patients with COPD, as olfactory dysfunction has been reported in allergic individuals [33].

The effect of smoking on the olfactory function is controversial. Some studies report impaired olfactory function in smokers [34, 35] and a meta-analysis from 2017 concludes that current smoking, but not former smoking, is associated with significantly increased risk of olfactory dysfunction, and that the effects of smoking on olfaction may be reversible [36]. Other studies report that smoking has no major effect on the olfaction [37-39]. In our study, the number of non-smokers (n=5) in the COPD group and current smokers (n=7) in the control group were low, and we could not perform reliable statistical computations on such numbers. Among the former smokers, we found that TDI, T, D and I were significantly lower in COPD compared to controls. Dinc et al. [40] found a significant improvement in D, I, and TDI scores after smoking cessation. However, this improvement was inversely associated with the duration of smoking, indicating that a longer duration of smoking may result in an insufficient improvement after smoking cessation.

This study shows that patients with COPD have a limited subjective awareness of the sense of smell. Whereas 79% had hyposmia or anosmia by the "Sniffin' Sticks" test, only 30% of patients reported impaired olfactory function (Figure 2b). In COPD, nasal symptoms are underestimated, and sometimes they are neglected, as the disease is thought to be limited to the lungs [2, 7] and other and more prominent symptoms of the disease, like cough and dyspnoea, demand more attention in everyday life. However, there is clinical- and epidemiological evidence that the united airways disease concept also applies in COPD [4, 5, 7, 41, 42]. It is therefore important that otolaryngologists and pulmonologists are aware of upper airways symptoms and olfactory dysfunction in COPD patients.

One unanticipated finding in our study was that the prevalence of parosmia and phantosmia in the control group was not significantly different from the COPD group. The prevalence of

parosmia and phantosmia as stand-alone symptom in population studies are both estimated at ~ 4% [43, 44], and with higher estimates up to 32% in patients with different clinical conditions [44]. In this study, the diagnosis of parosmia and phantosmia was question based, and the high prevalence of parosmia and phantosmia in both the COPD and control groups emphasizes the importance of measuring hedonic olfactory perception using validated tools and not only patient reported outcome.
The prevalence of anosmia and hyposmia in the control group in the present study was higher than the prevalence reported in a similar age span in a normal population [20]. Nevertheless, the results of our study show that patients with COPD suffer from reduced olfactory function, and this should be taken into consideration when evaluating the upper airways in patients with COPD.

Strengths and limitations

The present study has many strengths. Confirmation of the COPD diagnosis excludes the inclusion of asthma and ACO. Secondly, obvious pathology and anatomical abnormalities that could affect the ability to smell were excluded by nasal endoscopy. Thirdly, the large sample size of both groups and age- and sex adjusted controls give statistical strength to the results. Finally, the "Sniffin' Sticks" panel evaluates different aspects of the olfactory processing and function, whereas the UPSIT is restricted to evaluation of identification.
The study also has limitations. Firstly, we were unable to investigate the interaction between smoking, CRSsNP and olfactory function due to the low number of non-smokers in the COPD group and current smokers in the control group. Smoking is the leading cause of COPD [22] and may affect olfaction [23], thus it would have been desirable to have had statistical strength to include an interaction term. Secondly, CT of the sinuses was not performed, and a CRSsNP diagnosis could have been missed in symptomatic cases with a normal endoscopy. However, there is no clear consensus that a sinus CT examination is essential for a diagnosis of CRS in these subjects [15]. Thirdly, the absence of an association between CRSsNP and the TDI score may be due to a type 2 error, as the prevalence of CRSsNP in the control group was 16%. Finally, a validated self-reported olfactory questionnaire was not used, and the use of such a questionnaire would have strengthened the findings of the study [45].

Generalisability

COPD is associated with olfactory dysfunction. The underlying mechanisms for this dysfunction in COPD should be elucidated to give a better understanding of the clinical significance for this large group of patients.

Conclusion

In this study, we found that the olfactory function (TDI) assessed with the "Sniffin' Sticks" was significantly lower in COPD compared to a control group. Of the odour subtests, discrimination and identification were lower in COPD than in controls, while the threshold subtest did not differ between the groups. CRSsNP was not associated with TDI or any of the 3 component scores.

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Authorship contribution

"WMT: Study design, data collection, statistical analysis, paper drafting; SBD: Study design, data collection, paper drafting; MRØ: Study design, data collection, paper drafting; MSC: Study design, paper drafting; SKS: Study design, paper drafting; ASH: Study design, statistical analysis, paper drafting.

Conflict of interest

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