Sinonasal inflammation in COPD: a systematic review

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ABSTRACT In this review, we demonstrate that patients with chronic obstructive pulmonary disease (COPD) frequently report sinonasal symptoms. Furthermore, we present evidence that smoking on its own can cause nasal disease and that, in COPD patients, nasal inflammation mimics that of the bronchi. All this evidence suggests that COPD-related sinonasal disease does exist and that smoking on its own rather than systemic inflammation triggers the condition. However, COPD-related sinonasal disease remains to be characterised in terms of symptoms and endoscopic findings. In addition, more studies are needed to quantify the negative impact of sinonasal symptoms on the quality of life in COPD patients.

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Introduction

Chronic obstructive pulmonary disease (COPD) is frequently a severe condition with a serious impact on quality of life (QoL), primarily as a result of poor respiratory performance. In fact, COPD symptoms are so alarming that they potentially camouflage co-existing health problems. In this review, we consider whether sinonasal disease constitutes such a co-existing health problem.

Disease of the lower and upper airways often co-exist which has led to the concept of the ''united airways''. This is well documented in individuals with atopic disease; however, pan-airway disease is also found in the absence of atopy, *e.g.* in patients with chronic rhinosinusitis (CRS) and nonallergic rhinitis (NAR) [1, 2]. In COPD, the airway too appears to be united since patients with COPD frequently report sinonasal symptoms [3–5].

Sinonasal inflammation in COPD might develop in response to lower airway disease as a result of circulating pro-inflammatory cytokines and systemic inflammation or through neural reflexes. Alternatively, co-existing disease arises from the same histopathogenetic process initiated by tobacco smoke.

Therefore, we aim to perform a systematic literature review to investigate the associations between sinonasal disease and COPD as well as smoking.

Historically, there has been a lack of international consensus on how to define sinonasal disease and thus the nomenclature throughout the review varies considerably. Terms like ''chronic rhinosinusitis'', ''nonallergic rhinitis'', ''non-infectious rhinitis'' (NIR), ''allergic rhinitis'' or simply ''sinusitis'' will be encountered since they all represent sinonasal disease. Though this is confusing, a discussion of these terms would fall outside the scope of this review and recently, both in Europe and the USA, efforts have been made to simplify and standardise sinonasal disease classification [2, 6, 7].

Methods

An independent literature search using PubMed was performed on December 8 2011. We searched for the MeSH terms ''Nasal Polyps'', ''Rhinitis'' and ''Sinusitis'' in combination with ''Smoking'' and ''Chronic Obstructive Pulmonary Disease'', respectively, and restricted the search to English papers. This search resulted in 357 publications.

Publications were screened according to predefined selection criteria. We included all studies reporting on either COPD or smoking and sinonasal disease. We excluded studies that solely investigated children or adolescents, and studies that focused on atopic individuals exclusively.

Furthermore, we did not include studies that reported on smoking and the outcome of functional endoscopic sinus surgery (FESS). Several authors have reported on this issue [8]; nevertheless, we chose not to include such studies since we believe they constitute a poor model for smoking-induced nasal disease. In all fields of surgery, smoking is known or suspected to lead to worse outcomes because of delayed wound healing [9]. Hence, it is difficult to distinguish this general effect from a local effect in the nose.

The references were independently evaluated by two authors (K. Håkansson and L. Konge) and after a first consensus meeting, 46 articles were included, of which nine were review articles. The papers including their references were studied and after a second consensus meeting, 11 additional studies were included. Three additional papers known to the authors but not indexed by PubMed at the time of the search were also included.

Thus, we ended up with 51 original papers; the majority of these (60%) were published within the previous 10 years. Table 1 shows these papers including their design, year of publication, sample-size and use of objective measurements (or lack thereof).

Smoking and sinonasal disease

In 1973, WILSON [10] found that cigarette smokers more frequently reported bronchitis, emphysema, and sinusitis than never smokers in a study based on a sample of 42,000 households. Furthermore, COMSTOCK *et al.* [11] found persistent nasal catarrh to be more prevalent among present smokers compared with non-smokers; smoking cessation, on the other hand, reduced this problem. These historical papers have since been supported by numerous studies.

In a recent European multicentre study comprising 57 128 participants, present smoking was significantly associated (OR 1.91) with CRS and there was evidence of a dose-dependent relationship between number of pack-years and risk of having CRS [12]. NAR was also significantly associated with smoking in a large sample of 10 670 Swedish individuals [13] and in a smaller Danish sample (n=3471) [1]. However both studies were limited by questionnaires that did not discriminate between NAR and common cold. Another Swedish study reported that smoking was associated with an increased risk of non-infectious rhinitis (NIR) [14], a disease entity that includes both allergic rhinitis and NAR. Similar findings were reported from the USA and Greece [15, 16].

TABLE 1 Details of the studies included from the literature review

Study	Year	Design	Participants n	Allergy test	Nasal endoscopy	Lung function test
Smoking and sinonasal disease						
WILSON [10]	1973	Cross-sectional study	42 000 households	No	No	No
COMSTOCK *et al.* [11]	1970	Prospective cohort study	670	No	No	S
HASTAN *et al.* [12]	2011	Cross-sectional study	57 128	No	No	No
OLSSON *et al.* [13]	2003	Cross-sectional study	10 670	No	No	No
HÅKANSSON *et al.* [1]	2011	Cross-sectional study	3471	Yes	No	S
HELLGREN *et al.* [14]	2002	Cross-sectional study	2044	No	No	No
TURKELTAUB *et al.* [15]	1991	Cross-sectional study	12 742	No	No	No
SICHLETIDIS *et al.* [16]	2005	Cross-sectional study	6112	No	No	S
ANNESI-MAESANO *et al.* [17]	1997	Prospective cohort study	191	Yes	No	No
ANNESI *et al.* [18]	1992	Cross-sectional study	324	Yes	No	P
COLLINS *et al.* [19]	2002	Prospective and retrospective case series	1020	No	Yes[#]	No
HOUSER *et al.* [20]	2008	Retrospective case series study	474	Yes	Yes	No
REH *et al.* [21]	2009	Case-control study	200	No	No	No
EBBERT *et al.* [22]	2007	Case-control study	1007	No	No	No
LIEU *et al.* [23]	2000	Cross-sectional study	20 050	No	No	No
MIN *et al.* [24]	1996	Cross-sectional study	9069	No	Yes	No
SIRACUSA *et al.* [25]	1997	Cross-sectional study	824	Yes	No	No
Smoking and its effect on the nasal mucosa						
TAMASHIRO *et al.* [26]	2009	Randomised controlled laboratory study		No	No	No
DAVIS *et al.* [27]	2010	Randomised controlled laboratory study		No	No	No
MAHAKIT *et al.* [28]	1995	Descriptive study	140	Yes	No	No
PIOTROWSKA *et al.* [29]	2010	Descriptive study	63	Yes[#]	Yes	S
WOOD *et al.* [30]	1997	Descriptive study	46	No	No	No
PLAVEC *et al.* [31]	1993	Descriptive study	144	Yes	No	No
SMALL *et al.* [32]	1994	Descriptive study	52	Yes	No	No
LAINE-ALAVA *et al.* [33]	1999	Descriptive study	249	No	No	No
SYABBALO *et al.* [34]	1986	Descriptive study	105	No	No	S
STROUD *et al.* [35]	1999	Descriptive study	47	No	No	No
KJÆRGAARD *et al.* [36]	2010	Cross-sectional study	2523	No	No	No
TARP *et al.* [37]	2000	Descriptive study	404	No	No	No
KEIGER *et al.* [38]	2003	Descriptive study	24	No	No	No
BENDE *et al.* [39]	1998	Prospective study	33	No	No	No
GOLDSTEIN-DARUECH *et al.* [40]	2011	Randomised controlled laboratory study	34	No	No	No
OLIN *et al.* [41]	1998	Descriptive study	73	No	No	S
COPD and sinonasal disease						
CHEN *et al.* [42]	2003	Cross-sectional study	73 364	No	No	No
MONTÉMERY *et al.* [43]	1992	Cross sectional study	8469	No	No	No
NIHLÉN *et al.* [44]	2008	Cross sectional study and follow up study	4280	No	No	No
HURST *et al.* [45]	2006	Descriptive study	51	No	No	S
KELEMENCE *et al.* [5]	2011	Descriptive study	90	No	No	S
VAN MANEN *et al.* [46]	2001	Descriptive study	290	No	No	S
ROBERTS *et al.* [4]	2003	Descriptive study	61	No	No	S
CORSICO *et al.* [47]	2007	Descriptive study	212	No	Yes[¶]	S+B+A[¶]
KIM *et al.* [48]	2007	Descriptive study	73	Yes	Yes	S+B+A
RAGAB *et al.* [49]	2004	Descriptive study	25	Yes	Yes	S+B+A
Inflammatory changes of the nasal and bronchial compartments						
HURST *et al.* [50]	2006	Descriptive study	41	No	No	S+B
HURST *et al.* [51]	2005	Descriptive study	59	No	No	S+B
VACHIER *et al.* [52]	2004	Descriptive study	28	Yes	Yes	No
HENS *et al.* [53]	2008	Descriptive study	151	Yes[¶]	Yes	Yes
RAGAB *et al.* [54]	2005	Descriptive study	25	Yes	Yes	S
NIHLÉN *et al.* [55]	2003	Descriptive study	49	Yes	No	S+B
COPD, smoking and sinonasal QoL						
HURST *et al.* [3]	2004	Descriptive study	65	No	No	S+B
DAS *et al.* [56]	2009	Prospective study	235	No	Yes	No

S: spirometry performed; P: provocation; B: bronchodilator test performed; A: airway hyperresponsiveness tested. [#]: performed but the method is not described in the paper; [¶]: performed on some participants but not systematically.

Furthermore, two studies of a cohort of Parisian policemen showed that smoking was significantly more prevalent among subjects with chronic rhinitis (OR 5) independent of allergy status [17, 18].

COLLINS *et al.* [19] and HOUSER *et al.* [20] independently investigated the association between nasal polyps and smoking in two studies comprising 1020 and 373 patients, respectively. Both studies included patients undergoing surgery for nasal polyposis and they found the prevalence of smoking among nasal polyp patients to be 50–100% higher than in the background population. In addition, HOUSER *et al.* [20] reported that CRS without polyposis was not associated with smoking.

The role of second-hand smoke (SHS) exposure in sinonasal disease has also been investigated. In a case–control study, REH *et al.* [21] found a significant association between CRS and SHS exposure either in childhood or at the time of the study. Furthermore, CRS cases that had been exposed to SHS reported more

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severe symptoms. Unfortunately, the two groups were not matched for atopy. These findings were supported by a study on flight attendants. EBBERT *et al.* [22] showed that more hours in a smoky cabin was significantly associated with sinusitis, but the study was weakened by a low response rate (14%). Still, study results about the association between SHS and sinusitis are ambiguous. LIEU *et al.* [23] reported no association between sinusitis and SHS exposure in a large sample (n=20 050); instead they found an association between sinusitis and present tobacco consumption. The diagnosis of sinusitis was unsupported by clinical examinations in both this study and the one from EBBERT *et al.* [22].

Two groups did not find an association between smoking and sinonasal disease [24, 25]. SIRACUSA *et al.* [25] studied 824 individuals; however, 70% of the rhinitis cases in this study had allergic rhinitis and no separate analysis was performed for the nonallergic cases. MIN *et al.* [24] examined 2899 households (n=9069) in Korea in 1996 and found a prevalence of chronic sinusitis of 1%; smoking was not a determining factor. The criteria for having chronic sinusitis in this study were stringent since three out of four symptoms (nasal obstruction, hyposmia, facial pain, rhinorrhoea) were needed for the diagnosis. Furthermore, nasal polyps or purulent discharge had to be present at the time of examination and since whole families were examined, the mean age was low. This stringency might explain the low prevalence of 1% and, overall, these findings indicate that smoking does not induce gross endoscopic abnormalities.

In summary, both cross-sectional and clinical studies suggest an association between smoking and nasal symptoms.

Smoking and its effect on the nasal mucosa

The effect of smoking on the nasal mucosa has been described in multiple studies and a broad variety of techniques and outcome measures have been applied. In this section, *in vitro* nasal mucosa studies, studies of smoking and mucociliary clearance as well as nasal hyperresponsiveness and microbiology will be discussed.

Two *in vitro* studies have investigated the effect of tobacco smoke on nasal mucosa cells. TAMASHIRO *et al.* [26] found that both the particulate and the volatile phase of tobacco smoke impaired the ciliogenesis in a dose-dependent manner. The smoke components were administered through the baso-lateral compartment of the cells; this mimics toxins arriving through the bloodstream but not the direct effect of tobacco smoke passing over the nasal mucosa. DAVIS *et al.* [27] suggested that tobacco smoke activates complement and thereby initiates cell damage. *In vitro* exposure of nasal mucosa to tobacco smoke-induced membrane depositions of complement on human respiratory epithelial cells when cultured in serum. Furthermore, cell damage after smoke exposure was less pronounced in complement deficient mice compared to wild type.

Smoking is generally presumed to affect the mucociliary clearance. MAHAKIT *et al.* [28] analysed mucociliary transit time using the saccharin test in controls, in patients with allergic rhinitis or sinusitis, and in smokers. Sinusitis patients and patients who had been smoking more than one pack a day for more than 5 years had a markedly prolonged transit time. Smokers in this study visited the clinic ''with another nasal problem''; this problem is not elaborated and might on its own have contributed to the reduced clearance. Nevertheless, these findings were later supported by PIOTROWSKA *et al.* [29]. Alterations of nasal mucins have been speculated to contribute to the prolonged mucociliary clearance. This was investigated by WOOD *et al.* [30], who did not find changes in the sulfation of nasal mucins in allergic rhinitis or in smokers.

A few studies about smoking, nasal resistance and nasal hyperresponsiveness have been performed. PLAVEC *et al.* [31] compared a group of workers and patients (n=84) occasionally exposed to respiratory irritants along with a group of controls (n=60) and found that smoking was inversely related to nasal responsiveness; these finding were later supported by SMALL *et al.* [32]. In a study of 249 individuals without any nasal symptoms, LAINE-ALAVA *et al.* [33] found that smoking was associated with lower nasal cross-sectional areas [33]; furthermore, other studies have found smoking to increase nasal resistance [34, 35]. Finally, KJÆRGAARD *et al.* [36] found a reduced mucosal compliance in smokers which might explain the decrease in nasal responsiveness and patency. However, the mucosal changes caused by smoking must be discrete since TARP *et al.* [37] did not find smoking to be associated with any mucosal changes on magnetic resonance imaging in 404 patients suspected to have intracranial neurological pathology.

Nicotine receptor gene expression in the nasal mucosa has been demonstrated [38], and perhaps nicotine receptor activation somehow influences the mucosal compliance. One study found that smoking cessation in patients with chronic rhinitis did not improve the minimal cross-sectional area after 20 weeks when smoking was substituted with nasal nicotine; unfortunately, no controls were enrolled [39]. However, the role of nicotine receptors in the nasal mucosa is completely unknown.

The role of bacteria and biofilms in CRS is controversial. GOLDSTEIN-DARUECH *et al.* [40] investigated how tobacco smoke affects the biofilm-forming capacity of bacteria and showed that bacteria obtained from the

nasal cavity of smokers exist in a phenotypic state capable of biofilm formation in the presence of tobacco smoke. In contrast, bacteria from nonsmokers did not possess such a capacity. By either exposing bacteria to tobacco smoke or sham, the phenotypes could be reversed. This might indicate that CRS is initiated or modulated by biofilm-forming bacteria in smokers; alternatively, it simply confirms that bacteria can adapt to stressful environments by forming biofilms.

Nitric oxide (NO) is found in high concentrations in the sinuses and is believed to play a role in the immune defence against bacteria as well as being a cell signalling molecule [2]. Fractional exhaled nitric oxide (*Fe*NO) is a standardised test to monitor lower airway disease and *Fe*NO is reduced in smokers [57]. Measurement of nasal NO on the other hand, is not a standardised test; nevertheless, one study found nasal NO to be reduced in smokers [41]. This indicates lower levels of NO in the nose and sinuses and thus a change in the bacterial milieu of the upper airways.

In summary, smoking has been proven to damage nasal epithelial cells *in vitro*. Furthermore, clinical studies report smoking to reduce nasal mucociliary clearance and nasal hyperresponsiveness whilst increasing nasal resistance. Finally, smoking possibly affects the bacterial milieu directly or through a reduction in nasal NO.

COPD and sinonasal disease

In the largest cross-sectional study to date (n=73 364), CHEN *et al.* [42] found CRS to be associated with smoking, and obstructive lung diseases, such as asthma and COPD. Furthermore, a large study from Sweden (n=8 469), reported that one-third of the participants had sinonasal symptoms; among those with asthma and chronic bronchitis/emphysema, 46% and 40%, respectively, had nasal symptoms as well. For the group of patients with asthma, nasal symptoms were induced by pollen, animals and mould, whereas patients with chronic bronchitis/emphysema experienced nasal symptoms when exposed to dust, damp/cold air and stress [43]; these findings were later reproduced in a study from Sweden by NIHLEN *et al.* [44]. These three studies were all limited by the use of self-reported disease and as we pointed earlier, this is a common problem (table 1). However, not all studies support an association between COPD and sinonasal disease. We studied NAR and lower airway disease in an unselected Danish population. In a sample of 3471 participants, we found NAR to be associated with asthma (OR 2.51), chronic bronchitis (OR 2.27), and poor lung function. The association with chronic bronchitis was stronger in NAR than in allergic rhinitis, whereas the opposite was true for asthma. We did not find NAR to be associated with COPD but this might have been due to poor classification of sinonasal disease as a result of our questionnaire [1]. Furthermore, SICHLETIDIS *et al.* [16] found a marked association between smoking and rhinitis but rhinitis was not significantly more prevalent among individuals with COPD.

The majority of clinical studies on COPD and sinonasal disease have been performed by researchers with a background in respiratory medicine. HURST *et al.* [45], a group from England that has contributed markedly to this area of research over the past 10 years, showed that nasal airway obstruction mirrors the impairment of pulmonary airflow in 51 former *and* present smokers with mild–severe COPD. In 2011, KELEMENCE *et al.* [5] studied the frequency of sinusitis in patients with COPD; 90 patients (COPD stage I–IV) were included and 48 (53%) had sinusitis. Furthermore, VAN MANEN *et al.* [46] found a strong association between irreversible airway obstruction and sinusitis (OR 6). Unfortunately, neither study discriminated between chronic and acute sinonasal disease. ROBERTS *et al.* [4] examined sinonasal complaints in 61 patients with moderate–severe COPD of whom about 90% had a history of smoking. They found a high prevalence of nasal symptoms (75%) irrespective of smoking status (former/present smoker); however, the study did not include a standardised questionnaire for sinonasal disease, nor did it include nasal endoscopy. Furthermore, higher endoscopic scores and more symptoms were found in COPD patients (both present and former smokers) by PIOTROWSKA *et al.* [29]. Finally, CORSICO *et al.* [47] found an association between CRS and COPD stage 0+, a potentially reversible condition that may or may not be an early form of COPD. However, COPD stage 0+ could more appropriately be classified as chronic bronchitis without irreversible airway obstruction.

In Korea, KIM *et al.* [48] investigated lower airway disease in 73 patients with CRS and found only two cases of COPD (2.7%) compared with asthma (11%), bronchial hyperresponsiveness (AHR) (7%), small airway disease (SAD) (15%), and bronchiectasis (5%). This signifies that, in Korea, the prevalence of COPD in CRS patients is comparable or lower than in the background population [58] even though 47.9% of the patients were smokers. Unfortunately, it is unclear how many of the patients, who had nasal polyps or whether they were referred in preparation for surgery. RAGAB *et al.* [49] found lower airway involvement such as asthma and SAD in 60% of 25 CRS patients who failed medical treatment; however, the study design did not allow distinction between nonreversible asthma and COPD.

In summary, cross-sectional studies indicate that COPD and bronchitis are associated with nasal disease but the evidence is somewhat ambiguous; nonetheless, clinical studies unanimously found sinonasal complaints to be common among COPD patients. However, the majority of studies on sinonasal disease in COPD

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patients either did not include controls or they did not use standardised diagnostic criteria for sinonasal disease. Furthermore, to date, no clinical study has found an increased prevalence of COPD in patients with sinonasal disease.

Inflammatory changes of the nasal and bronchial compartments

Patients with exacerbation of COPD (n=41) or stable disease (n=47) were studied by HURST and colleagues [50, 51]. Sputum, nasal lavage fluid, and blood were analysed for biomarkers. They found evidence of a pan-airway inflammation during exacerbations in which the degree of upper airway inflammation correlated with the degree of lower airway inflammation. The levels of myeloperoxidase (MPO) paralleled each other in nasal lavage fluids and sputum; furthermore, nasal interleukin (IL)-8 was increased in stable COPD and correlated with sputum IL-8. Of note, no controls were enrolled in the first of the above studies by HURST *et al.* [50] and the second one did not use induced sputum systematically. VACHIER *et al.* [52] compared mild–moderate COPD (n=14) with smoking (n=7) and nonsmoking controls (n=7) and found higher numbers of neutrophils in both nasal and bronchial mucosa of COPD patients without nasal symptoms. These findings were partly supported by HENS *et al.* [53] who examined nasal inflammation in lower airway disease. The study comprised 90 patients (allergic asthma (n=35), nonallergic asthma (n=24) and COPD (n=31)) with stable disease and 61 healthy controls. COPD patients reported more nasal symptoms and showed signs of nasal inflammation with increased levels of eotaxin, granulocyte colony-stimulating factor and interferon-γ in nasal secretions; IL-8 on the other hand was unchanged compared to controls. All three patient groups showed signs of nasal inflammation and differences between COPD and asthma patients (with or without allergy) were small. Interestingly, higher levels of eotaxin and normal IL-8 indicates an eosinophilic response, which contrasts with HURST and colleagues [50, 51], who found increased levels of IL-8 and a correlation between nasal and bronchial MPO indicating a neutrophilic response. The three studies used diverse techniques for sampling and none of the studies investigated both MPO and eotaxin. Finally, PIOTROWSKA *et al.* [29] examined nasal inflammation in COPD by measuring leukotrienes in nasal lavage fluids and despite reporting higher nasal endoscopic scores in COPD patients, no difference in leukotriene concentrations compared with controls was found.

RAGAB *et al.* [54] studied the cytology of middle meatal lavage (MML) and bronchoalveolar lavage (BAL) in 25 CRS patients; 14 had nasal polyposis. Asthma and SAD was found in six and nine patients, respectively; nonetheless, COPD cases could have been overlooked as we elaborated above. In the asthma subgroup, eosinophils were dominant in MMLs, whereas in the SAD subgroup, neutrophils were dominant. Overall there was no significant correlation between inflammatory types in MML and BAL samples.

NIHLÉN and co-workers have performed two studies within this field. In a paper from 2003 they studied 23 COPD patients and 26 controls of whom 10 and five, respectively, reported nasal symptoms; nasal lavages were obtained before and after histamine challenge [55]. COPD was not associated with any marked nasal inflammation though increased neutrophilic activity was suggested. The study design included rigorous lavage before sampling which could have diluted the biomarkers in focus. Furthermore, patients with CRS were excluded from the study even though nasal inflammation in COPD patients might clinically present as CRS. This is underlined by the same group in 2008 where they found that continuous thick yellow discharge and nasal blockage predicted later development of chronic bronchitis (OR 2.3) and COPD (OR 1.8) [44]. In addition, VACHIER *et al.* [52] contradicted the earlier study by NIHLEN *et al.* [55] when they found a correlation between nasal and bronchial inflammation despite the exclusion of patients with nasal symptoms.

In summary, only three studies, comprising 102 patients in total, aimed to compare inflammation of the nose and lungs in COPD patients and all of them found signs of neutrophillic inflammation throughout the airway. Three studies (n=104) solely investigated nasal inflammation in COPD and only one study found inflammatory changes that indicated an eosinophilic response.

COPD, smoking and sinonasal quality of life

HURST *et al.* [3] investigated the impact of upper airway symptoms on the QoL in 65 patients with moderate–severe COPD. The St. George Respiratory Questionnaire (SGRQ), a QoL questionnaire specific to COPD, and the Sino-Nasal-Outcome-Test-20 (SNOT-20) was used, and 88% experienced nasal symptoms on most days of the week, most commonly rhinorrhoea. Interestingly, there was no significant correlation between SNOT-20 and SGRQ, suggesting that upper and lower airway symptoms independently affect the QoL in COPD patients. The SNOT-20 questionnaire was also used in 90 COPD patients living in Turkey [5]. Sinonasal symptoms were present in 53% and SNOT-20 scores were significantly higher in more severe cases of COPD. However, this latter difference must be interpreted with caution since it primarily stemmed from higher scores in questionnaire subsets that would have been affected by changes in lower airway symptoms.

Finally, DAS *et al.* [56] examined the QoL in a prospective study of 235 (21.3% smokers) undergoing surgery (FESS). SNOT-20 scores were obtained before and after surgery. This study showed similar preoperative SNOT-20 scores in smokers and nonsmokers.

In summary, studies describing the impact of sinonasal symptoms on the QoL in COPD patients are sparse. Only two such studies have been performed; one of them indicates a true independent negative impact, whereas the other one does not.

Discussion

There are some weaknesses to the studies reviewed in the present analysis. Many of them lack proper clinical examination of the nasal cavity, the lungs or both (table 1) even though allergy testing, nasal endoscopy and spirometry with bronchodilator test or bronchial provocation are vital in the evaluation of diseases of the upper and lower airways.

No allergy test illustrates allergy entirely; nevertheless, a standard skin prick test is often the most favourable to use. Studies that do not include an allergy test cannot discriminate strictly between allergic rhinitis and nonallergic nasal disease, as such. This constitutes a problem since smoking might have different or even opposing effects in allergic rhinitis and nonallergic disease [1, 13, 15]. Several studies in this review did not include allergy testing [15, 16, 21, 25]. Likewise, some studies did not include nasal endoscopy and therefore could not discriminate between nasal disease with or without nasal polyps [21, 48]. This too is troublesome because nasal disease with and without nasal polyps may be differently associated with smoking. COLLINS *et al.* [19], HOUSER *et al.* [20] and others have found smoking to be associated with nasal polyposis, a disease that is generally considered to be eosinophilic in nature, at least in Caucasians [59]. However, other studies have shown that sinonasal inflammation in COPD is skewed towards a neutrophilic response resembling CRS without nasal polyps [50–52, 60]. Hence, it is unclear whether smoking is associated with nasal polyps or not and more studies based on a strict up-to-date classification and methodology are needed.

Inadequate objective measurements or weak disease classification might better be prevented in future studies if they are carried out in collaboration between specialties (ear–nose–throat (ENT) and respiratory medicine). Otherwise, researchers tend to fulfil guidelines and diagnostic criteria within their own field (either upper or lower airway disease) but fail to do so for the opposing end of the airway [1, 4, 18, 44–46].

Of course, these demands for objective measurements cannot always be met in large cross-sectional studies and TOMASSEN *et al.* [61] recently found that symptom-based CRS was in fact significantly associated with positive findings on nasal endoscopy. This indicates that nasal endoscopy perhaps, could be left out in studies that use standard questionnaires which ensure enough information to classify nasal disease. In the study by TOMASSEN *et al.* [61], questions based on the European Position Paper on Rhinosinusitis and Nasal Polyps (EP3OS) criteria were used. None of the cross-sectional studies discussed in this review included such well-designed questions. For example, both OLSSON *et al.* [13] and our group [1] used questionnaires that did not allow certain distinction between simple colds, chronic disease or simply nasal septal deviations. In our previous study, sinonasal questions were part of a larger survey and hence they were reduced to a minimum [1]. This is a frequent problem in large cross-sectional studies as they often aim to describe a wide variety of diseases [23, 42].

Estimating the impact on the QoL is important when trying to evaluate the importance of any disease; nevertheless, detecting a reduction in QoL as a result of sinonasal disease in COPD patients is difficult. The SNOT-20 and 22 are validated questionnaires that are frequently used in sinonasal disease; however, approximately 50% of these questionnaires are unspecific to the nose and thus potentially influenced by lower airway disease. KELEMENCE *et al.* [5] reported a difference in SNOT-20 scores from COPD stage I–II compared with stage III–IV patients. This finding arose solely from unspecific questions such as sleep difficulties, fatigue and reduced productivity. This is a general problem when evaluating nasal disease and its impact on QoL since it so often co-exist with lower airway disease, *e.g.* the united airways. Nonetheless, HURST *et al.* [3] found no correlation between SNOT-20 and the SGRQ, which indicates a true negative impact of nasal symptoms in COPD patients.

Probably, smoking has numerous effects on the nasal mucosa; some are immediate and potentially reversible, some are slowly progressive and persistent. If an analogue to COPD exists in the sinonasal cavity, we would expect such a disease to be chronic and partly irreversible. VAN MANEN *et al.* [46] found that the association between irreversible airway obstruction and sinusitis was independent of smoking status (former or present). Furthermore, WILSON *et al.* [10] found that former and present smokers reported the same increased rates of sinusitis (15%), and increased rates of sinonasal disease among former smokers compared with never-smokers were reported by others [12, 13, 18, 42]. Likewise, HURST *et al.* [45] found that nasal airway obstruction mirrors the impairment of pulmonary airflow in both present and former smokers.

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Finally, several studies have found a dose–response relationship between smoking and sinonasal disease [1, 12, 17, 22, 26]. All this evidence indicates a causal and long lasting effect of smoking. Conversely, COMSTOCK *et al.* [11] found that males who quit smoking showed a reduction in nasal symptoms over time which demonstrates that the effect of smoking is reversible to some extent.

Unfortunately, for the purpose of this review, nearly all investigated COPD patients were ever or present smokers. COPD in never-smokers is controversial and probably does not exist outside of developing countries. Therefore, an isolated effect of COPD on the upper airways cannot be evaluated. Hence, alternative explanations for sinonasal involvement in COPD such as systemic inflammation and neural reflexes are plausible too.

Finally, clinical researchers outside respiratory medicine with an interest in COPD face the common problem of referral bias. This calls for attention, not least in clinical studies on lower airway disease in patients with sinonasal disease. Often such patients are referred to the ENT clinic in preparation for surgery, *e.g.* RAGAB *et al.* [49]. However, patients with moderate–severe COPD might never get referred for surgical procedures because of their poor respiratory performance and this obviously causes bias. Furthermore, in the case of sinonasal disease, nasal symptoms might simply never get recognised because of the complexity and severity of COPD. KIM *et al.* [48] did not state if patients were referred in preparation for surgery or not, but for reasons mentioned above, this is important to know. Referral bias might explain why no study has found COPD to be prevalent in an ENT population with sinonasal disease.

In conclusion, surprisingly few studies have addressed the association between smoking or COPD, and sinonasal disease, and the majority of them are small. Clearly, sinonasal symptoms are more frequently reported by COPD patients compared to the background population. Furthermore, evidence suggests that smoking, in a dose-dependent manner, induces nasal symptoms and inflammation and in COPD patients, the nasal and bronchial inflammation are comparable. All this evidence strongly suggests that COPD related sinonasal disease does exist and that smoking, at least to some extent, triggers the disease.

However, COPD related sinonasal disease remains to be characterised in terms of symptoms, endoscopic findings and type of inflammation. In addition, it remains to be established whether COPD patients actually consider sinonasal disease to be a significant problem that requires treatment and potentially, a new QoL questionnaire that can isolate the impact of sinonasal symptoms in COPD patients more convincingly is needed. Thus, future research in COPD calls for a closer collaboration between ENT specialists and respiratory physicians as it has already been proposed for other ''united airway'' diseases.

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