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Sino-Nasal Characteristics in Asthmatic Patients

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Abstract

Objective. The Unified Airways Hypothesis suggests an involvement of the upper airways in asthma. We aimed to evaluate the association between subjective sino-nasal complaints, nasal air flow, and sino-nasal quality of life (QOL) in patients with asthma compared with nonasthmatic subjects.

Study Design. Case-control study.

Setting. A tertiary referral center.

Subjects and Methods. Symptoms, quality of life, and nasal air flow were assessed in 91 asthmatics and 95 nonasthmatic controls with Visual Analog Scale (VAS, 0–100), Sino-Nasal Outcome Test (SNOT-20), and Peak Nasal Inspiratory Flow (PNIF), respectively. Asthma and allergy status were assessed by Asthma Control Questionnaire (ACQ) and skin prick test or specific IgE.

Results. Asthmatic patients (men/women, 37/54; mean age, 43.7 years; range, 19–64 years) reported significantly more nasal obstruction (mean VAS, 37 mm; SD = 26, 95% CI, 32–43 vs 9 mm, SD = 11, 95% CI, 7–11, $P < .001$) and lower sino-nasal quality of life (mean SNOT-20, 1.3; SD = 0.8, 95% CI, 1.1–1.5 vs 0.4, SD = 0.5, 95% CI, 0.3–0.5, $P < .001$) than controls (men/women, 42/53; mean age, 43.8 years; range, 20–65 years). PNIF was significantly lower in asthmatic patients than controls (mean PNIF, 84 l/min; SD = 24, 95% CI, 79–89 vs 100 l/min SD = 24, 95% CI, 95–105, $P < .001$).

Conclusion: Both allergic and nonallergic asthma were associated with increased sino-nasal symptoms, reduced sino-nasal QOL, and reduced inspiratory nasal air flow compared to controls. This provides further evidence of the clinical importance of the upper airway in the diagnostic and therapeutic management of asthma patients beyond the scope of allergy.

Keywords

allergy, asthma, rhinitis, sinusitis, quality of life

The concept of the Unified Airway Hypothesis considers the entire respiratory system from the nose and paranasal sinuses, larynx, trachea, and large and small airways as one integrated unit.¹ It has become increasingly clear that inflammation in the upper respiratory tract affects the lower respiratory tract and vice versa. Over 75% of adult patients with allergic and nonallergic asthma have symptoms of rhinitis.² The coexistence of asthma with allergic rhinitis is associated with more severe asthma symptoms, reduced asthma-related quality of life, and greater problems controlling the lower airway symptoms.³ Conversely, 20% to 50% of patients with rhinitis have asthma.⁴ An increase in nonspecific bronchial responsiveness is seen in patients with allergic rhinitis without manifest asthma.⁵

There are several potential pathophysiological links between the upper and lower airways. Inhalation of

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allergens leads to local IgE-mediated inflammatory reactions both in the nose and bronchi in sensitized individuals. In rhinitis, sympathetic and parasympathetic signals are generated in the nose that may have pathophysiological influence on the bronchial tree.⁶ Nasal patency is a key feature in rhinitis, and oral breathing is a consequence. The consequent lack of cleaning, warming, and humidification of the air during inspiration may harm the lungs. The nose represents an important source of resistance for the lower airways during expiration. Mouth breathing, secondary to nasal obstruction may even in this perspective have a negative impact on the lungs.⁷

Although the concept of the unified airway is based on evidence from epidemiological, pathophysiological, and treatment outcome studies,⁸ there are limited studies that have investigated the upper airway characteristics in asthmatic patients using subjective and objective tools. In the study by Hens et al, increased nasal symptoms, reduced sino-nasal quality of life (QOL), and nasal inflammation were seen in asthmatic patients with and without allergy.⁹

Optimal diagnosis and treatment of nose problems in asthma patients are likely to improve QOL and reduce morbidity and asthma medication. Thus, it is important to learn about nose- and sinus-related symptoms and quality of life in these patients. In this study we investigated sino-nasal symptoms, nose- and sinus-related quality of life, and nasal airflow in allergic and nonallergic asthma patients.

Methods

Subjects. The study population consisted of 91 patients with asthma and 95 nonasthmatic controls.

The asthma diagnosis was based on the presence of typical asthma symptoms and variable airflow obstruction and in accordance with the British Thoracic Society criteria.¹⁰ Variable airflow obstruction was defined as an increase of $\geq 12\%$ and ≥ 200 mL in the forced expiratory volume in the first second (FEV1) from baseline after administration of salbutamol or a positive bronchial provocation test, defined as the provocative dose of methacholine of ≤ 1600 μ g that causes a fall in FEV1 of at least 20% from baseline.

Exclusion criteria were pregnancy, a history of cancer, presence of acute and chronic rhinosinusitis (CRS), and nasal polyposis on otorhinolaryngological examination, previous nasal surgery, and systemic disease with potential affection of the nose, such as Wegener's granulomatosis, cystic fibrosis, primary ciliary dyskinesia, Kartagener's syndrome, and sarcoidosis.

Written informed consent was obtained from all subjects. The study was approved by the National Ethical Committee of Norway and investigations were performed in accordance with the principles of the Declaration of Helsinki/Hong Kong. All subjective and objective recordings were performed between June 2009 and December 2010 in a controlled environment using trained personnel and modern equipment. Allergic control subjects were not included in the

pollen season (May–August) and asthmatic subjects were investigated between September 2009 and February 2010.

Subjective Measures

Questionnaire. Data on sex, weight, height, smoking habits, allergies, and medication were collected in a self-administered questionnaire.

Symptoms. The degree of nasal obstruction (NO), oral breathing, snoring, sleep apnea, nasal discharge/secretions, headache, mid facial pain, rhino-sinusitis, coughing, sneezing, reduced general health, and reduced sense of smell was assessed on a 100 mm Visual Analog Scale (VAS). The endpoints were 0 mm (never) and 100 mm (always).

Quality of life. This was assessed with the Sino-Nasal Outcome Test-20 (SNOT-20) questionnaire, which is a validated disease-specific QOL questionnaire for rhino-sinusitis.¹¹ Subjects were asked to grade 20 items on a scale of 0 (no problem) to 5 (problem as severe as can be). The SNOT-20 score for each subject was defined as the mean value of the response to the 20 items. Furthermore, the SNOT-20 questionnaire was divided into subsets based on the study of Browne et al.¹² The first subset was composed of the questions about the symptoms related to nose, ear, and face; the second subset included the questions on psychological issues; and the third subset addressed sleep function. Questions about cough and waking up tired are separate entities and do not belong to any subset.

Asthma control. Asthma control in asthmatic subjects was assessed with the Asthma Control Questionnaire (ACQ), which is a validated disease-specific test used for evaluation of asthma symptoms.¹³

Clinical Investigation. A complete otorhinolaryngological examination with emphasis on the anatomic and functional aspects of the nose was performed.

Objective Measures

Allergy. Skin prick tests (Soluprick SQ, ALK-Abello, Horsholm, Denmark) or specific IgE (AlaTOP, Diagnostics Products Corp., Los Angeles, California) for pollen (birch, grass, and mugwort), cladosporium, house dust mite (*Dermatophagoides pteronyssinus*), and animal epithelia (horse, dog, and cat) were performed. Use of antihistamines was discontinued 4 days prior to skin prick tests. Subjects with positive tests and typical symptoms of hypersensitivity on exposure to the allergen(s) were classified as allergic.

Nasal airflow. This was assessed noninvasively by measuring the Peak Nasal Inspiratory Flow (PNIF, L/min) during forced inspiration with a portable PNIF meter (In-check DIAL, Clement Clarke International, Harlow, UK) prior to measurement of lung function. The maximum PNIF that can be measured with this meter was 120 L/min. PNIF in excess of this value was recorded as 120 L/min. The mean value of 3 satisfactory maximal nasal inspirations was calculated.

Lung function. Lung function was assessed by flow-volume spirometry (Spirostar USB spirometer, Medikro Oy,

Table 1. Demographic Data and Medical History on Asthmatic Patients and Controls

Characteristics	Asthmatic Patients (n = 91)	Controls (n = 95)
Mean age, y (range)	43.7 (19-64)	43.8 (20-65)
Mean BMI, kg/m ² (SD)	26.7 (4.9)	25.3 (3.4)
Sex		
Male, n (%)	37 (41)	42 (44)
Allergy	56/91 (62)	21/95 (22)
Pollen, n (%)	47/56 (83)	21/21 (100)
Animal dander, n (%)	41/56 (73)	9/21 (42)
House dust mite, n (%)	19/56 (34)	2/21 (10)
Smoking, n (%)	8 (9)	12 (13)
Samter's triad, n (%)	0 (0)	0 (0)
Medication		
Intranasal steroids, n (%)	31 (34)	0 (0)
Antihistamines, n (%)	30 (33)	5 (5)
ICS, n (%)	11 (12)	0 (0)
LABA, n (%)	4 (4)	0 (0)
Combined ICS and LABA, n (%)	75 (82)	0 (0)
Anticholinergic medication, n (%)	6 (7)	0 (0)
Leukotriene receptor antagonists, n (%)	18 (20)	0 (0)
Oral steroids, n (%)	6 (7)	0 (0)

Abbreviations: BMI, body mass index; ICS, inhaled corticosteroids; LABA, long-acting β_2 agonist.

Kuopio, Finland) before and 10 minutes after administration of 0.4 mg salbutamol in a spacer (Ventoline, Volumatic, GlaxoSmithKline, Middlesex, UK). The best FEV1 in liters and percentage of predicted¹⁴ of 3 acceptable attempts before and after salbutamol was recorded, in accordance with international guidelines.¹⁵

Statistics. The number of participants included in the study was based on power calculations. To obtain 80% power, we needed 100 participants in each group at a significance level of 0.05 (alpha) and given a difference in SNOT-20 of 0.4 between the groups. If the difference is 0.5 the estimated power was 94%.

Data are presented as mean, standard deviation (SD), and 95% confidence interval (95% CI). To evaluate differences in mean values we used independent samples *t* test. To assess the correlation between ACQ score and SNOT-20 and between ACQ score and NO-VAS, we used linear regression.

All statistical analysis was performed using PASW Statistics, version 18 for Windows (SPSS Inc., Chicago, Illinois).

Results

Demographic data, allergy, smoking status, and use of intranasal steroids, antihistamines, and asthmatic medication are presented in **Table 1**. Allergy was present in 62% of asthmatic patients and 22% of controls.

Subjective Measures

Symptoms. The VAS for each symptom was significantly greater in asthmatic patients than in controls (**Table 2**). The asthma patients had a mean VAS of the 12 sino-nasal symptoms of 30 (SD = 14, 95% CI, 27-33) and the control group

11 (SD = 9, 95% CI, 9-12), $P < .001$. As to nasal obstruction, the asthmatic patients had a mean NO-VAS of 37 (SD = 26, 95% CI, 32-42) and the controls 9 (SD = 11, 95% CI, 7-11), $P < .001$ (**Figure 1**).

Quality of life. The asthmatic patients had a significant impairment of their nose and sinus-related quality of life (**Table 3**). The mean SNOT-20 score in asthmatic patients was 1.3 (SD = 0.8, 95% CI, 1.1-1.5) and in the control group 0.4 (SD = 0.5, 95% CI, 0.3-0.5), $P < .001$. Comparison of SNOT-20 scores for each question in the asthma group and control group showed highly significant differences for all questions, $P < .001$, except ear pain ($P = 0.1$). The scores for rhinologic, ear/facial, sleep function, and psychological function subsets showed statistical significance between asthmatic patients and controls in all subset scores ($P < .001$).

Asthma control. The asthma patients had an ACQ score of 1.6 (SD = 1, 95% CI, 1.4-1.8).

Clinical Investigation. The investigation confirmed that the asthmatic patients and the controls included in the study did not have symptoms or signs of CRS or nasal polyposis.

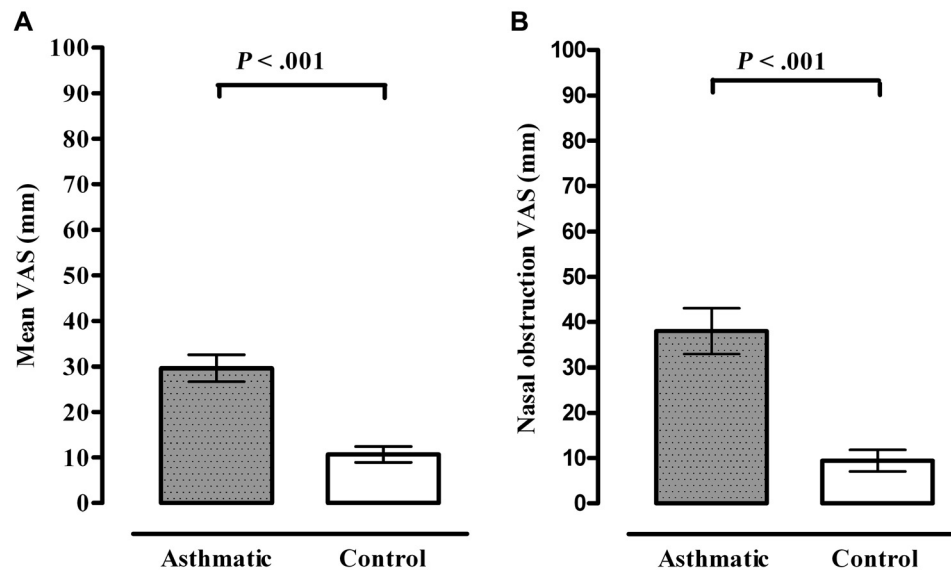
Objective Measures

Allergy. Mean VAS score, NO-VAS, SNOT-20, and PNIF were significantly greater in allergic asthmatic patients than in allergic controls and in nonallergic asthmatic patients than in nonallergic controls (**Figure 2**).

Nasal airflow. The baseline mean PNIF in asthmatic patients was 84 (SD = 24, 95% CI, 79-89) and among the controls 100 (SD = 24, 95% CI, 95-105), $P < .001$.

Table 2. Visual Analog Scale (VAS) Scores for Sino-Nasal Symptoms in Asthmatic Patients and Controls: Values Presented as Mean (SD)

Symptom	Asthmatic Patients (N = 91)	Controls (N = 95)	P
Nasal obstruction	37 (26)	9 (11)	< .001
Oral breathing	47 (29)	13 (22)	< .001
Snoring	40 (33)	26 (29)	.004
Sleep apnea	15 (27)	7 (17)	.02
Nasal discharge/secretions	28 (23)	11 (18)	< .001
Headache	32 (28)	16 (21)	< .001
Mid-facial pain	15 (21)	9 (17)	.033
Rhino-sinusitis	12 (21)	4 (8)	< .001
Coughing	41 (31)	7 (9)	< .001
Sneezing	39 (26)	15 (17)	< .001
Reduced general health	27 (29)	5 (8)	< .001
Reduced sense of smell	24 (27)	5 (10)	< .001

**Figure 1.** Symptoms described by the mean Visual Analog Scale (A) and Nasal Obstruction Visual Analog Scale (B) in the asthmatic patients (gray) and controls (white). Values presented as mean, 95% CI.

Lung function. The asthma patients had a mean pre FEV1 value of 80% predicted (SD = 18, 95% CI, 76-84) and the control group 96% predicted (SD = 13, 95% CI, 94-99), $P < .001$.

Association of SNOT-20 and NO-VAS with ACQ. Linear regression analysis showed that the ACQ score increased by 0.76, per unit increase in SNOT-20 (95% CI, 0.52-0.97) and by 0.12 (95% CI, 0.5-2.0) per 10 unit increase in NO-VAS.

Discussion

In this study we have demonstrated that asthma patients have more sino-nasal symptoms and lower sino-nasal QOL and

PNIF compared to the controls. These findings also apply to asthmatic patients and controls, irrespective of their allergy status. In addition, quality of life and nasal obstruction are correlated with the degree of asthma control, and FEV1 percentage predicted is significantly lower than in controls. The findings of increased sino-nasal symptoms and lower QOL in our study are in agreement with the study by Hens and coworkers.⁹ However, we have also shown that asthmatic patients have a reduced sense of smell and general health.

The higher level of NO-VAS in the asthmatic patients compared with the controls may be caused by nasal obstruction among the former. The recently demonstrated correlation between subjective and objective nasal obstruction

Table 3. Comparison of Sino-Nasal Outcome Test (SNOT-20) Scores for Each Question and Subset in Asthmatic Patients and Controls: Values Presented as Mean (SD)

Question	Asthmatic Patients (n = 91)	Controls (n = 95)	P
Need to blow nose ^a	1.9 (1.3)	0.6 (0.8)	< .001
Sneezing ^a	1.6 (1.2)	0.5 (0.7)	< .001
Runny nose ^a	1.4 (1.2)	0.4 (0.7)	< .001
Cough	1.9 (1.4)	0.3 (0.7)	< .001
Postnasal discharge ^a	0.9 (1.3)	0.2 (0.6)	< .001
Thick nasal discharge ^a	1.0 (1.2)	0.2 (0.5)	< .001
Ear fullness ^b	1.3 (1.3)	0.6 (1.1)	< .001
Dizziness ^b	1.1 (1.2)	0.4 (0.8)	< .001
Ear pain ^b	0.6 (1.0)	0.4 (0.9)	.100
Facial pain/pressure ^b	0.8 (1.2)	0.2 (0.5)	< .001
Difficulty falling to sleep ^c	1.2 (1.4)	0.3 (0.9)	< .001
Wake up at night ^c	1.7 (1.4)	0.7 (1.2)	< .001
Lack of good night's sleep ^c	1.8 (1.5)	0.6 (1.2)	< .001
Wake up tired	2.2 (1.4)	1.0 (1.8)	< .001
Fatigue ^d	1.3 (1.4)	0.3 (0.7)	< .001
Reduced productivity ^d	1.5 (1.5)	0.2 (0.6)	< .001
Reduced concentration ^d	1.5 (1.4)	0.4 (0.7)	< .001
Frustrated/restless/irritable ^d	1.4 (1.5)	0.3 (0.7)	< .001
Sad ^d	0.8 (1.2)	0.2 (0.5)	< .001
Embarrassed ^d	0.5 (1.0)	0.1 (0.3)	< .001
Subset			
Rhinologic ^a	1.4 (0.8)	0.4 (0.4)	< .001
Ear/facial ^b	0.9 (0.9)	0.4 (0.7)	< .001
Sleep function ^c	1.6 (1.2)	0.5 (0.9)	< .001
Psychological function ^d	1.2 (1.1)	0.3 (0.5)	< .001
Mean SNOT-20	1.3 (0.8)	0.4 (0.5)	< .001

^aQuestions belonging to rhinologic subset.^bQuestions belonging to ear/facial subset.^cQuestions belonging to sleep function subset.^dQuestions belonging to psychological function subset.

makes such an assumption fair.¹⁶ The reduced PNIF in the asthma group compared with the controls supports this, as it also has been shown that there is a correlation between the subjective sense of nasal patency and objective nasal airflow.¹⁷ Nasal obstruction may principally be due to either structural and/or mucosal abnormalities. We have deliberately chosen not to classify the extent of septal deviations, turbinate hypertrophy, or other structural deformities as there is a lack of standardized classification systems and as the very subjective, investigator-dependent, and descriptive nature of such data severely limits their scientific transfer value.

As it is less likely that there should be a systematic increased incidence of structural abnormalities in the asthmatic patients' noses, the nature of such an obstruction probably is mucosal. This is in line with the theory that the link between asthma and rhinitis involves a generalized mucosal inflammation affecting both the upper and lower airways, including a mucosal edema in the nose.¹⁸ However, perception of nasal obstruction may have different etiologies as it depends not only on flow alone, but on nasal

cavity dimensions, thermal receptors, pressure receptors, pain receptors, secretions, change in mood, sinus congestion, and Eustachian tube function as well.¹⁹ The sensation of nasal airflow is primarily based on a cool sensation in the nose rather than to sensations from the lungs and respiratory muscles.²⁰ The increased experience of nasal obstruction in asthmatic patients might be a result of less stimulation of these receptors. This assumption is supported by the reduced PNIF in the asthmatic patients.

PNIF is based on forced inspiration and reduced forced inspiration may give reduced stimulation of the sensors for nasal airflow. Low PNIF values may be an expression of low ventilatory activity rather than an expression of nasal obstruction. Accordingly, the subjective nasal obstruction reported by the asthmatic patients may not be a reflection of nasal pathology per se, but of a reduced pulmonary ventilatory capacity as shown by reduced FEV1 percentage values.

The coexistence of rhinitis and asthma in allergic individuals is well recognized by clinicians. However, we found significant greater VAS for sino-nasal symptoms, NO-VAS,

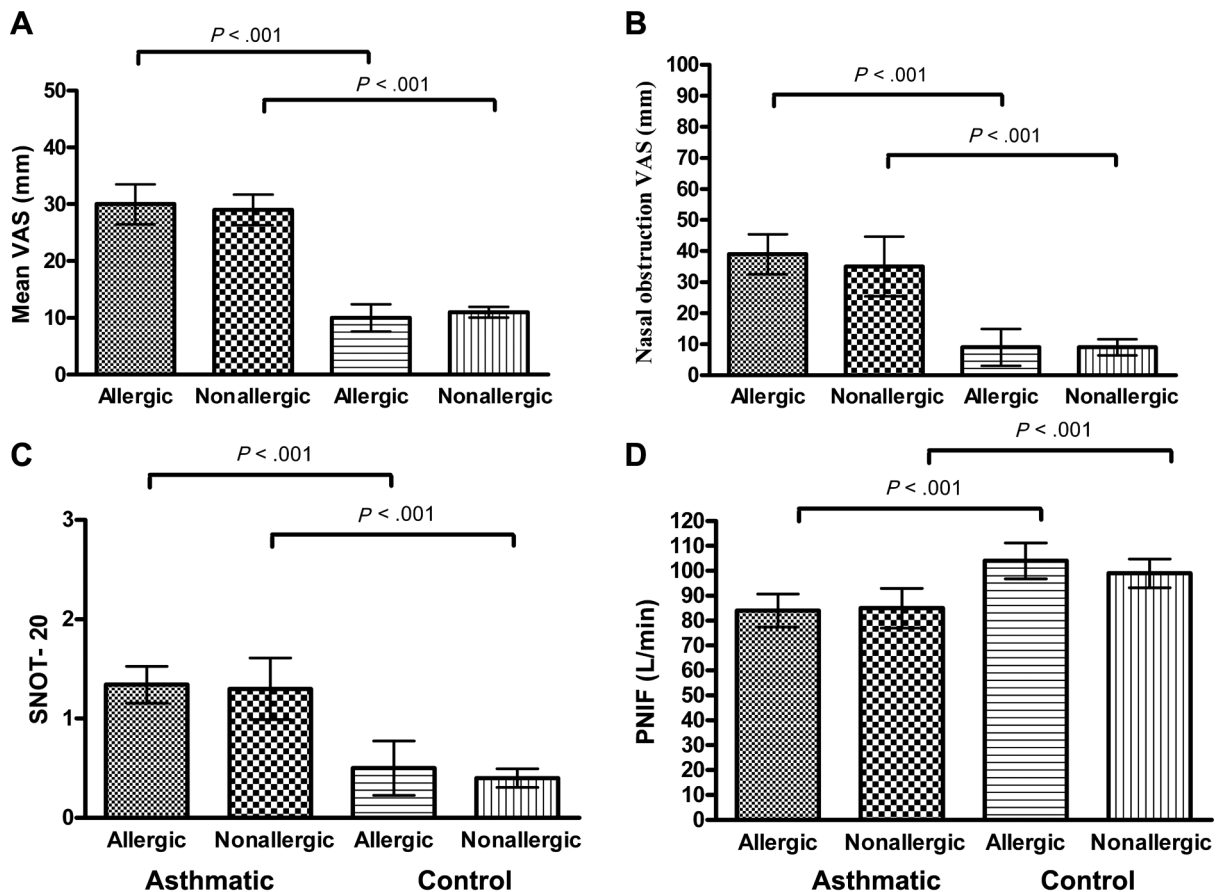


Figure 2. Mean VAS (A), NO-VAS (B), SNOT-20 (C), and PNIF (D) in allergic asthmatic patients, nonallergic asthmatic patients, allergic controls, and nonallergic controls. Values presented as mean, 95% CI. Abbreviations: VAS, Visual Analog Scale; NO-VAS, Nasal Obstruction Visual Analog Scale; SNOT-20, Sino-Nasal Outcome Test; PNIF, Peak Nasal Inspiratory Flow.

SNOT-20, and PNIF in nonallergic asthmatic patients who were assessed outside of the pollen season, compared with nonallergic controls (**Figure 2**). Similar findings have been reported by Hens et al⁹ and highlight the importance of a thorough otorhinolaryngological examination, with particular focus on the anatomic and functional aspects of the nose, and evaluation in all asthma patients, irrespective of the presence or absence of airway allergy.

It is well acknowledged that the coexistence of rhinitis and asthma appears to impair asthma control.² The ACQ score in the present study corresponds well to the ACQ scores of other comparable studies.²¹ The positive correlation between ACQ score and SNOT-20 and NO-VAS scores provides further evidence in support of the relationship between poor asthma control and sino-nasal symptoms and quality of life in asthmatic patients.

The asthma patients have a reduced sino-nasal QOL as reported by SNOT-20. As expected, the asthma patients had lower SNOT-20 score compared with patients with CRS who have a SNOT score of 1.9.¹¹ Despite this, subgroup analysis shows a threefold increase in SNOT-20 score in the allergic asthmatic patients and nonallergic asthmatic

patients, compared with their respective controls. This is in line with our clinical experience, where patients with asthma have less sino-nasal problems compared with patients with CRS but still have serious upper airway malfunctions that affect their sino-nasal QOL. Thus SNOT-20 may also be a useful tool for the assessment of QOL, health status, and treatment response in asthmatic patients.

Analysis of the SNOT-20 questionnaire by subsets may suggest that differences in SNOT-20 scores between asthmatic patients and controls can be due to sleep disturbances. The ACQ score in the asthmatic patients is suggestive of relatively poor asthma control that can be associated with sleep disturbance.²² However, the difference between the asthma and control groups remained highly significant with P values $< .001$, when sleep questions were excluded from the SNOT-20 questionnaire. Moreover, asthmatic patients scored significantly higher on all questions in the SNOT-20, with the exception of the question concerning the presence of ear pain (**Table 3**).

The use of VAS, SNOT-20, and PNIF as tools to assess sino-nasal characteristics has some limitations. VAS may be limited, primarily because of its simplicity, while SNOT-20 lacks questions about nasal obstruction and loss of smell

and taste. PNIF gives a global characterization of the nasal air flow, but does not give any information about the separate nasal passages or nasal airflow under resting conditions. In addition, it is influenced by a number of covariates, especially peak expiratory flow (PEF), age, sex, and height.^{23,24} However, VAS is a validated and established instrument for assessing a wide range of symptoms, including nasal congestion, nasal discharge, headache, snoring, rhinosinusitis, decreased olfaction, and facial pain,^{25,26} and SNOT-20 has been used in a number of medical and surgical studies.^{27,28} The results of the present study suggest that the multidimensionality of sino-nasal symptoms may be better characterized when these instruments are used in conjunction.

Conclusion. We have shown that both allergic and nonallergic asthma were associated with increased sino-nasal symptoms, reduced sino-nasal QOL, and reduced inspiratory nasal air flow. This supports previous observations emphasizing that nasal pathology should be considered in the diagnostic and therapeutic approach of asthma patients beyond the scope of allergy.

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Author Contributions

Wenche Moe Thorstensen, substantial contribution to design, acquisition of data, analyzing, and interpretation of data; drafting the article and final approval of the version to be published; **Vegard Bugten**, substantial contribution to design, acquisition of data, analyzing, and interpretation of data; revising the article and final approval of the version to be published; **Malcolm Sue-Chu**, substantial contribution to design, analyzing, and interpretation of data; revising the article and final approval of the version to be published; **Nils Petter Wold Fossland**, substantial contribution to design, analyzing, and interpretation of data; revising the article and final approval of the version to be published; **Pål Richard Romundstad**, substantial contribution to design, analyzing, and interpretation of data; revising the article and final approval of the version to be published; **Sverre Karmhus Steinsvåg**, substantial contribution to design, acquisition of data, analyzing, and interpretation of data; revising the article and final approval of the version to be published.

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