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ORIGINAL CONTRIBUTION

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Symptom burden and health-related quality of life in moderate to severe chronic rhinosinusitis with nasal polyposis*

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Abstract

Background: Chronic rhinosinusitis with nasal polyposis (CRSwNP) affects up to 4% of individuals. Common symptoms include nasal congestion/obstruction, nasal discharge, facial pain, and reduced sense of smell. This study describes patient- and physician-reported CRSwNP symptom burden and health-related quality of life (HRQOL) in a real-world clinical setting.

Methods: This multinational, geographically diverse, point-in-time survey invited physicians to evaluate 5 consecutive adults with confirmed bilateral moderate to severe CRSwNP (consecutive sampling) plus the next 2 patients with recurrent nasal polyps and ≥1 surgery for polyp removal (oversampling). Patients' and physicians' surveys were assessed in the entire consecutive sample and by categories of physician-determined CRSwNP severity, and by categories of asthma comorbidity (total sample). Patients' and physicians' responses were compared in a matched sample.

Results: The total sample of 1,782 patients comprised 1,296 (72.7%) from consecutive sampling and 486 (27.3%) from oversampling. Among the consecutive sample (mean age, 46.9 years), 1,122 (86.6%) had moderate and 174 (13.4%) had severe CRSwNP. Of 1,697 patients from total sampling with known asthma status, 708 (41.7%) had asthma and 989 (58.3%) did not. Patients' self-reported symptom frequency, severity, and burden on HRQOL worsened with increasing CRSwNP severity and comorbid asthma. Physicians underreported prevalence, severity, and impact of symptoms on daily activities compared with patients (matched sample).

Conclusion: Patients and physicians from real-world settings both described a considerable burden of CRSwNP, but physicians consistently reported fewer and less severe symptoms than patients. This suggests a more patient-centric view is needed when assessing CRSwNP symptom burden and HRQOL.

Key words: chronic rhinosinusitis, nasal polyposis, patient-reported outcomes, quality of life, real-world setting, symptom burden, EQ-5D, SNOT-22, WPAI, patient burden

Introduction

Chronic rhinosinusitis with nasal polyposis (CRSwNP) is an inflammatory condition estimated to affect up to 4% of the general population in the United States and Europe [(1)]. It is characterized by various symptoms, including nasal congestion or obstruction, nasal discharge that can be mucopurulent, facial pain, and reduced or loss of sense of smell [(1,2)]. CRSwNP presents with significant morbidity and is often associated with other respiratory conditions such as asthma [(3,4)], which occurs in up to 56% of cases of CRSwNP [(3)]. CRSwNP with comorbid asthma can be characterized by tissue eosinophilia and high local immunoglobulin E levels (which may make patients candidates for biologic treatments against this type 2 inflammation) [(5)] and confers a higher symptom burden and worse quality of life than

CRSwNP without comorbid asthma [4]. Additionally, the impact of CRSwNP on patients' health-related quality of life (HRQOL) has long been recognized [6–8]. Patients with CRSwNP of any severity have been found to have significantly lower physical and mental HRQOL than population norms [7] and a higher burden of emotional symptoms [8].

Despite the prevalence and significant morbidity of CRSwNP, data from patients' perspectives on symptom severity and impact on HRQOL are limited [6]. Moreover, evidence evaluating whether physicians' assessments of symptoms reflect patients' experience is lacking. Real-world assessments of symptoms and HRQOL burden associated with CRSwNP, with and without asthma, are needed from both patients' and physicians' perspectives to provide a holistic view of CRSwNP. We assessed the symptom burden and HRQOL of CRSwNP from the perspectives of physicians and patients with moderate to severe CRSwNP according to disease severity and comorbid asthma status. We further assessed the discordance between physician and patient reports of disease burden and HRQOL.

Materials and methods

Study design

This study analysed data collected by the Adelphi CRSwNP Disease Specific Programme (DSP)™, an independent, multicentre, point-in-time physician and patient survey conducted in Europe (France, Germany, Italy, Spain, and the United Kingdom), the United States, and Japan between 2018 and 2019. The DSP™ provides established methods for acquiring real-world observations of current clinical practice from physicians' and their patients' viewpoints, as published previously [9]. The survey received ethical exemption determination by the Western institutional review board, a centralised international board for the United States (Study Number: #1-1090610-1), Europe, and Japan (Study Number: #1-1162676-1).

Physician and patient selection criteria

Target specialist physicians (otolaryngologists, pulmonologists, allergists, and internists [Japan only]) from geographically diverse regions (recruitment proportional to population density) were identified from publicly available lists of health care providers. Information about physicians' practice specialty and workload was collected through an online survey to screen candidate participants for pre-established eligibility criteria. Eligible physicians were responsible for treatment decisions and cared for a minimum of 3 patients with moderate to severe CRSwNP per week. Physician participation was voluntary and compensated at a fair market value.

Enrolled physicians recruited patients aged ≥18 years with moderate to severe CRSwNP based on a physician-confirmed diagnosis. Physicians were advised to rely on their clinical expertise to establish a patient diagnosis. They were also provided with guidance for defining disease severity and determining nasal polyp (NP) scores according to the European Position Paper on Rhinosinusitis and Nasal Polyps, such as using visual analogue scale (VAS) symptom scores and endoscopy (with VAS >3–10 and presence of mucosal disease at endoscopy for moderate to severe CRSwNP) [2,10]. Physicians were instructed to complete a patient record form for 5 consecutive patients with the presence of bilateral, moderate to severe NPs (consecutive sample), followed by the next 2 patients with bilateral, recurrent NPs who had ≥1 previous surgery for polyp removal (oversample). The consecutive sample and oversample were collected independently and are mutually exclusive. The consecutive sample was representative of patients with CRSwNP seen in routine care practice, and the oversample was necessary to increase the proportion of patients with surgical history. The same patients were invited by their physicians, but not required, to fill out a patient self-completion form independently. Patients with physician-determined mild CRSwNP, aged <18 years, or currently participating in a clinical trial were excluded.

Outcome measures

The outcome measures were physician- and patient-reported presence of NP symptoms as well as scores of disease burden, symptom severity, and HRQOL. The patient record forms completed by physicians recorded enrolled patients' demographic and clinical characteristics at survey date, including selected comorbidities (type 2 inflammation), derived Charlson comorbidity index (CCI)—a measure of long-term mortality risk, with a lower score indicating lower risk [11,12], and current NP score—a physician-reported grade of the extent/severity of NPs, ranging from 0 (no polyps) to 4 (large, obstructive polyps) in each nostril. Physicians also reported their perceived current level of patients' overall disease severity (by checking either moderate or severe in response to the question "How would you rate the severity of this patient's nasal polyps, currently?"); presence of individual NP symptoms (by responding to the question "Thinking about this patient's nasal polyps symptoms in the last 2 weeks, which of the following nasal polyps symptoms are you aware this patient experiences? Select all that apply" and selecting from a list of 22 symptoms included in the patient-reported outcome instrument 22-item Sino-Nasal Outcome Test [SNOT-22] [13]); and impact level of symptoms (by selecting 1 response [as bad as can be, severe, moderate, mild, very mild, no problem, and not stated/don't know] to the question "How problematic have these symptoms been for the patient in terms of frequency and severity? Select one") on different aspects of daily life (i.e., work/education, leisure/sport, attending social events, being self-conscious in social situations, forming personal relationships, and having intimate relationships).

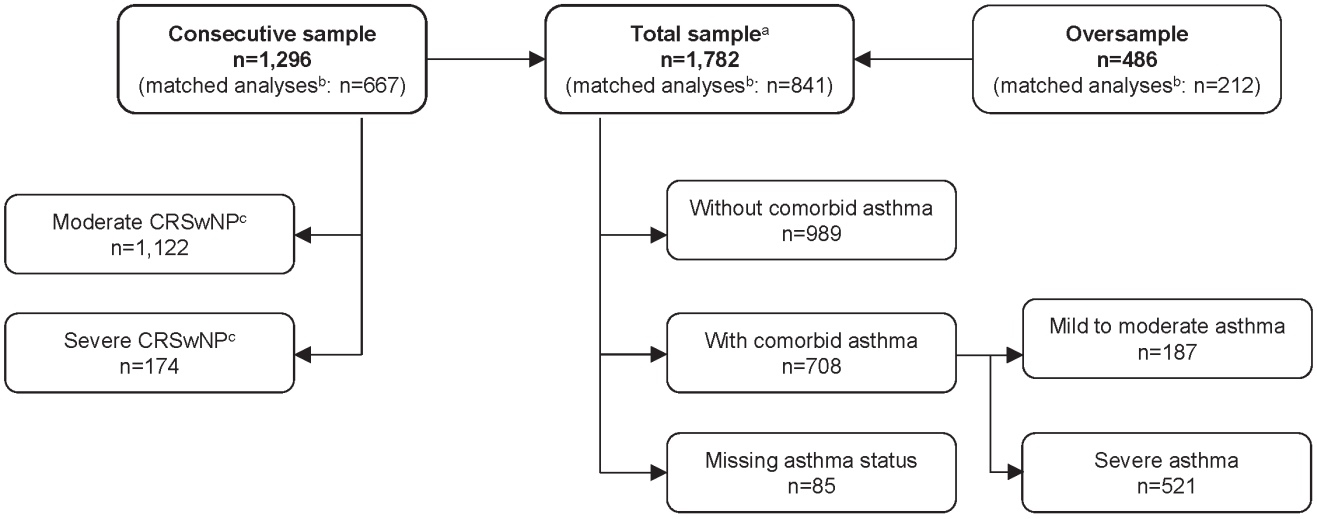

Figure 1. Flowchart of patient sampling and populations analysed.

[a] Included 1,127 patients from Europe (197 from France, 245 from Germany, 246 from Italy, 245 from Spain, and 194 from the United Kingdom), 351 from the United States, and 304 from Japan, that were recruited by 266 physicians (otolaryngologists, pulmonologists, allergists, and internists [Japan only]) including 165 from Europe (35 from France, 36 from Germany, 36 from Italy, 35 from Spain, and 23 from the United Kingdom), 52 from the United States, and 49 from Japan. [b] Number of patients with available data (who had both physician and patient forms completed) for matched analyses. [c] CRSwNP severity determined by physician for each patient based on physician's clinical expertise and provided guidance to follow the European Position Paper on Rhinosinusitis and Nasal Polyps guidelines [2,10] and NP size scoring systems. Abbreviations: CRSwNP, chronic rhinosinusitis with nasal polyposis; NP, nasal polyp.

Physicians also reported whether the patient had a confirmed diagnosis of asthma. Patients with asthma were further categorized by asthma severity at survey date using Global Initiative for Asthma (GINA) 2018 treatment step criteria [14]. Asthma was considered severe based on GINA steps 4 or 5 derived from currently prescribed therapy and level of inhaled corticosteroid dose (low, medium, or high). All other patients with asthma and GINA steps 1–3 were qualified as having mild to moderate asthma.

After providing informed consent, patients reported their overall rating of disease severity (mild, moderate, severe) and the symptoms (SNOT-22) they were experiencing [13] in the patient self-completion form. The form also captured the impact of symptoms using multiple questionnaires. The first questionnaire assessed the level of impact of symptoms on the same aspects of daily life as reported by physicians. Second, the work productivity and activity impairment (WPAI) questionnaire assessed the percentages of work time missed (absenteeism), work time impaired (presenteeism), overall work impairment (combination of absenteeism and presenteeism), and total activity impairment [15]. Finally, the SNOT-22 total score, ranging from 0 (lowest burden) to 110 (worst burden) [13], and EuroQoL visual analogue scale (EQ-VAS) score, ranging from 0 (worst imaginable health state) to 100 (best imaginable health state) [16], were used to assess the impact of symptoms on overall health status.

Analyses

Descriptive analyses were performed on means (SDs) for continuous variables and percentages of patients for categorical variables, without any formal statistical comparisons. Missing data were not imputed or included in calculations of percentages. Analyses were generated using IBM SPSS Data Collection Survey Reporter and performed by Adelphi Real World.

Overall assessments and analyses by categories of physician-determined CRSwNP severity (moderate, severe) were performed in the consecutive survey sample because it was reflective of the routine care population. Analyses by categories of asthma comorbidity status and asthma severity included all patients with available physician-confirmed data on asthma comorbidity status taken from the total sample population (consecutive sample and oversample) (Figure 1).

Physician- and patient-reported data were matched to allow direct comparisons of perspectives from physicians and patients on presence of symptoms and overall disease severity. Matched analyses were performed using physician-reported data limited to patients who had filled out self-completion forms to allow direct descriptive comparisons between the same patient population; they excluded patients who had not completed their self-completion forms. Matched physician/patient analyses were conducted for 6 different subgroups of patients: patients

Table 1. Patient demographic and clinical characteristics at survey date.

	Consecutive sample (n=1,296)			Total sample with comorbid asthma data (n=1,697)			
	Overall CRSwNP	Moderate CRSwNP [a]	Severe CRSwNP [a]	Without asthma	With asthma	With mild/ moderate asthma	With severe asthma
	(n=1,296)	(n=1,122)	(n=174)	(n=989)	(n=708)	(n=187)	(n=521)
Age, mean (SD), y	46.9 (15.9)	46.7 (16.1)	47.8 (14.7)	47.1 (15.6)	47.2 (15.4)	45.5 (14.5)	47.9 (15.7)
Male sex, n (%)	772 (59.6)	666 (59.4)	106 (60.9)	632 (63.9)	387 (54.7)	97 (51.9)	290 (55.7)
BMI, mean (SD)	25.4 (4.6)	25.4 (4.4)	25.7 (5.7)	25.3 (4.3)	25.8 (4.5)	25.3 (4.3)	26.0 (4.6)
Tobacco smoking status, n (%)							
Current	180 (13.9)	150 (13.4)	30 (17.2)	174 (17.6)	65 (9.2)	13 (7.0)	52 (10.0)
Former	274 (21.1)	238 (21.2)	36 (20.7)	194 (19.6)	167 (23.6)	35 (18.7)	132 (25.3)
Never	710 (54.8)	620 (55.3)	90 (51.7)	524 (53.0)	424 (59.9)	114 (61.0)	310 (59.5)
Unknown	132 (10.2)	114 (10.2)	18 (10.3)	97 (9.8)	52 (7.3)	25 (13.4)	27 (5.2)
Comorbid condition [b], n (%)							
Allergic rhinitis	631 (48.7)	543 (48.4)	88 (50.6)	384 (38.8)	459 (64.8)	106 (56.7)	353 (67.8)
Asthma	515 (39.7)	447 (39.8)	68 (39.1)	0 (0)	708 (100.0)	187 (100.0)	521 (100.0)
Atopic dermatitis	94 (7.3)	83 (7.4)	11 (6.3)	68 (6.9)	53 (7.5)	11 (5.9)	42 (8.1)
COPD	86 (6.6)	75 (6.7)	11 (6.3)	72 (7.3)	42 (5.9)	5 (2.7)	37 (7.1)
CCI [c], mean (SD)	0.16 (0.60)	0.16 (0.61)	0.11 (0.50)	0.18 (0.61)	0.14 (0.59)	0.14 (0.61)	0.14 (0.58)
Current NP score, mean (SD)	3.5 (1.9)	3.1 (1.7)	5.9 (1.7)	3.8 (2.1)	3.6 (2.1)	3.4 (2.1)	3.7 (2.0)

[a] CRSwNP severity determined by physician for each patient based on physician's clinical expertise and provided guidance to follow the European Position Paper on Rhinosinusitis and Nasal Polyps guidelines [2,10] and NP size scoring systems. [b] Comorbid conditions related to CRSwNP and reported in >5% of patients. [c] The CCI is calculated based on the presence of select comorbidities. Abbreviations: BMI, body mass index; CCI, Charlson comorbidity index; COPD, chronic obstructive pulmonary disease; CRSwNP, chronic rhinosinusitis with nasal polyposis; NP, nasal polyp.

with severe CRSwNP, patients with moderate CRSwNP, patients without comorbid asthma, patients with comorbid asthma, patients with comorbid mild/moderate asthma, and patients with comorbid severe asthma. A sensitivity analysis compared the demographic characteristics and CRSwNP severity of patients from the consecutive sample who had agreed to complete their self-completion forms (and were included in the matched physician/patient analyses) with those who had declined to complete a self-completion form (and were not included in the matched analyses).

Results

Patient sampling and subgroups

The total sample (N=1,782) comprised 1,296 (72.7%) patients from consecutive sampling and 486 (27.3%) from oversampling (Figure 1). The consecutive sample included 1,122 (86.6%) patients determined by their physicians to have moderate disease and 174 (13.4%) who had severe disease. Among those from the total sample who had physician-confirmed asthma comorbidity status (n=1,697), 989 (58.3%) did not have comorbid asthma and 708 (41.7%) had comorbid asthma, of which 521 (30.7%) presented with severe asthma and 187 (11.0%) with mild to moderate asthma per GINA treatment step criteria [14].

In all, 629 of the patients in the consecutive sample had matched patient- and physician-reported data; these patients were examined both as a whole group and in subgroups of CRSwNP severity (moderate vs. severe). Of the total sample, 841 patients had matched patient- and physician-reported data; these patients were examined in subgroups of asthma comorbidity status (without vs. with) and in subgroups of comorbid asthma severity (mild/moderate vs. severe).

Patient demographic and clinical characteristics

The consecutive sample population had a mean age of 46.9 (SD 15.9) years, with the majority being men (59.6%) and non-smokers (54.8%) (Table 1). The most prevalent comorbidities were allergic rhinitis (48.7%) and asthma (39.7%). No major differences were observed between patients with severe and moderate CRSwNP, although those with severe CRSwNP were slightly older (47.8 vs. 46.7 years), had a higher percentage of current smokers (17.2% vs. 13.4%), and had higher NP scores (5.9 vs. 3.1) than

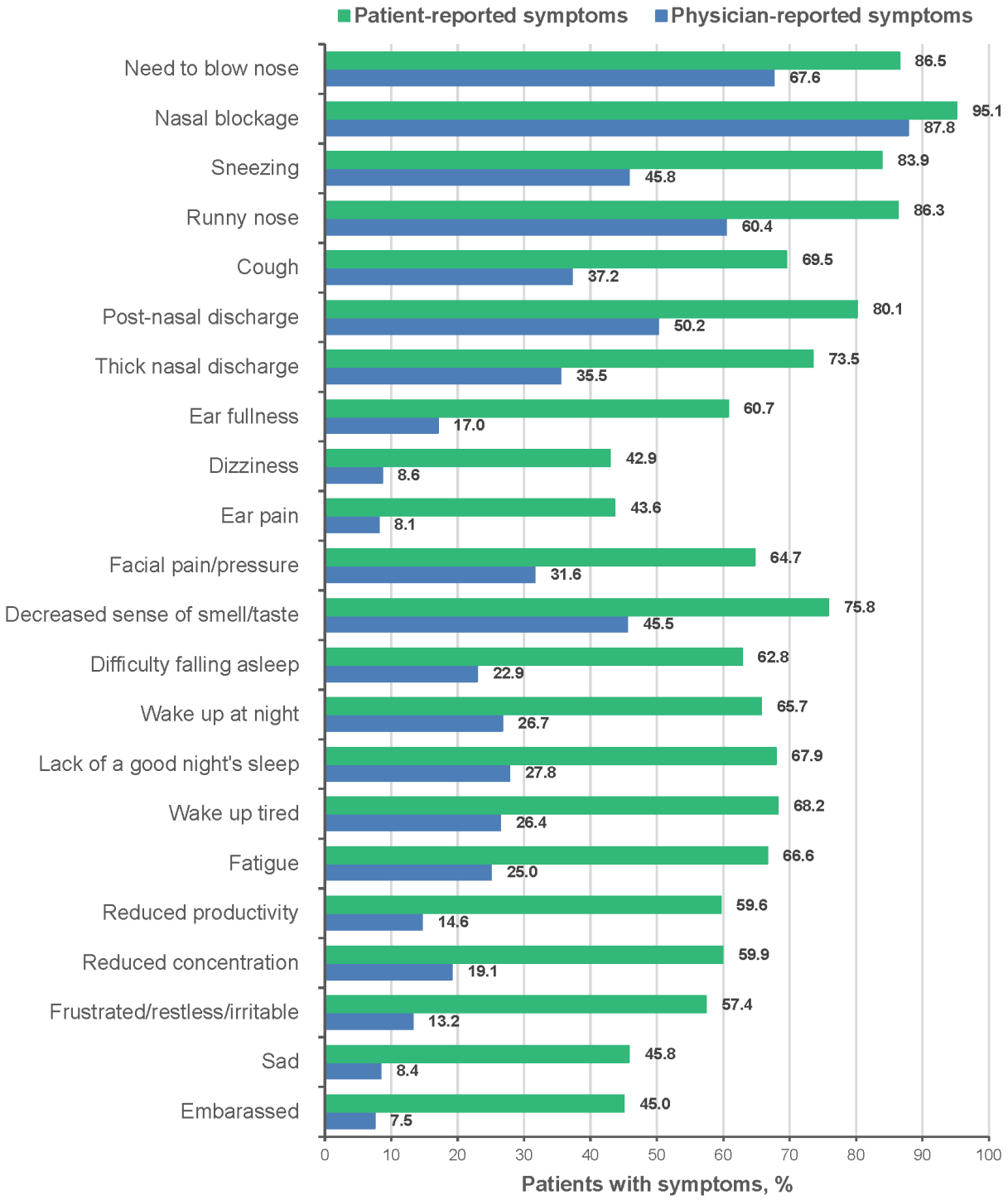

Figure 2. Prevalence of reported CRSwNP symptoms from matched patient/physician perspectives (consecutive sample, n=629). Abbreviation: CRSwNP, chronic rhinosinusitis with nasal polyposis.

patients with moderate CRSwNP.

Among 1,697 patients of the total sample population with available comorbid asthma data, mean age, overall CCI, and NP scores were similar among individuals without asthma, those with asthma, and those with severe asthma (Table 1). Patients with asthma were less frequently male (54.7% vs. 63.9%) and had a higher frequency of comorbid allergic rhinitis (64.8% vs. 38.8%)

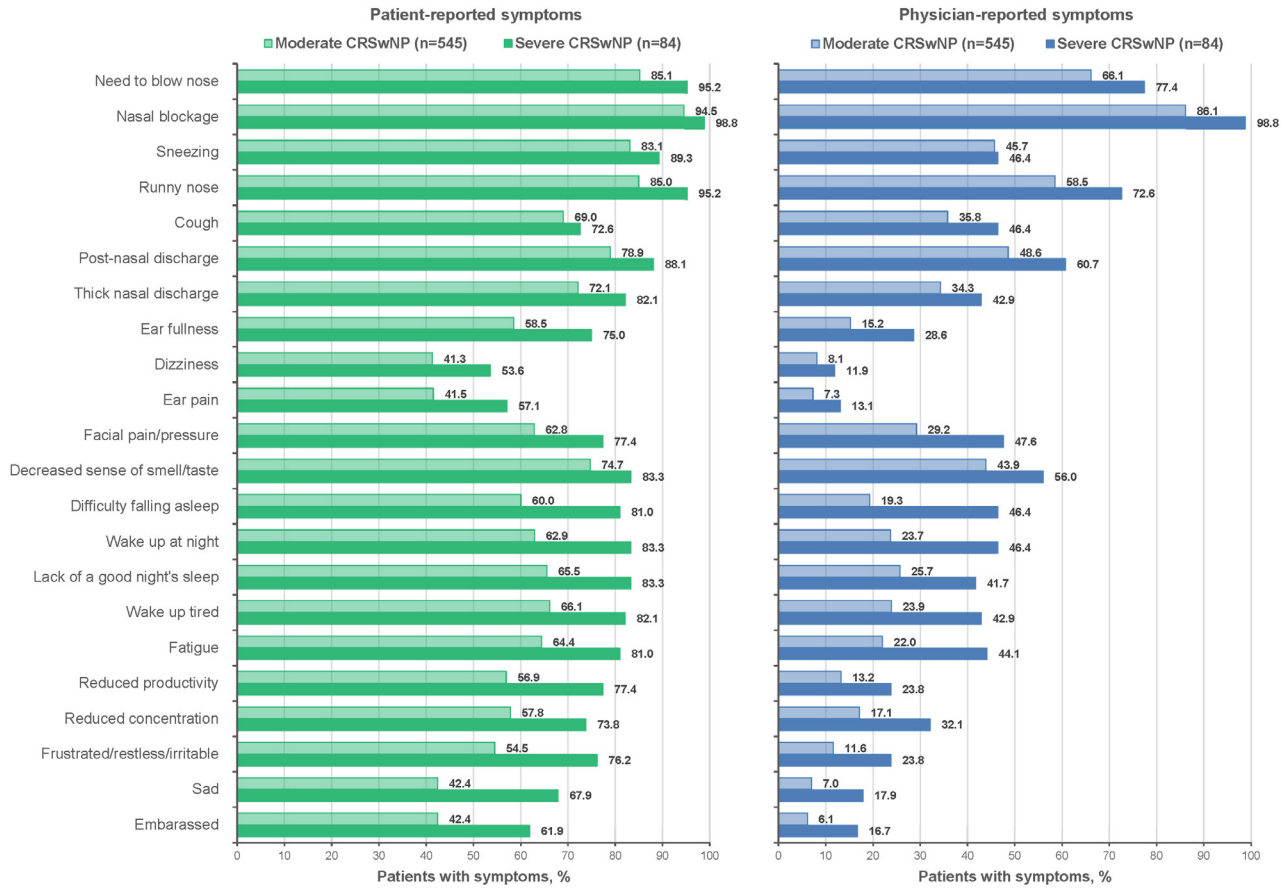

Figure 3. Prevalence of reported CRSwNP symptoms from matched patient/physician perspectives by categories of CRSwNP severity [a] (consecutive sample). [a] CRSwNP severity determined by physician for each patient based on physician's clinical expertise and provided guidance to follow the European Position Paper on Rhinosinusitis and Nasal Polyps guidelines [2,10] and NP size scoring systems. Abbreviations: CRSwNP, chronic rhinosinusitis with nasal polyposis; NP, nasal polyp.

than those without asthma. There were no significant differences in demographics or clinical characteristics noted between patients who completed the self-report forms (included in the matched analyses) and those who did not, with the exception of NP score (mean [SD] of 3.4 [1.9] vs. 3.6 [1.9]; p=0.046), presence of comorbid depression (6.3% vs. 3.5%; p=0.021), and racial/ethnic distribution (p=0.012) (Supplemental Table 1).

Burden of disease by categories of CRSwNP severity and asthma comorbidity

Patient- and physician-reported prevalence of symptoms and overall disease severity

Both patients and physicians most frequently identified the same top 3 symptoms as being experienced daily: nasal blockage, need to blow nose, and runny nose (matched analysis; Figure 2). The prevalence of patient-reported decreased sense of smell/taste was also high, and at least 42.5% of patients reported experiencing non-nasal and non-clinical symptoms (e.g., facial symptoms and impact on sleep, mental abilities, and emotional domains). Across all symptoms, the prevalence of patient- and physician-reported symptoms was always greater among those with severe CRSwNP than for those with moderate CRSwNP (Figure 3). Notably, non-nasal and non-clinical symptoms were reported at 10% to 20% higher frequencies by patients with severe versus moderate CRSwNP. Additionally, a greater proportion of patients determined by their physicians to have severe CRSwNP reported their overall disease to be severe compared with those determined to have moderate CRSwNP (72.3% vs. 18.5%; Figure 4).

Similar trends were observed among patients who had confirmed asthma status. The prevalence of patient-reported symptoms was greater among those with comorbid asthma compared with those without asthma (Supplemental Figure 1), and among those with severe comorbid asthma compared with those with mild/moderate comorbid asthma (Supplemental Figure 2). For example, nasal blockage, the most frequently reported symptom, was listed by 96.6% of patients with asthma

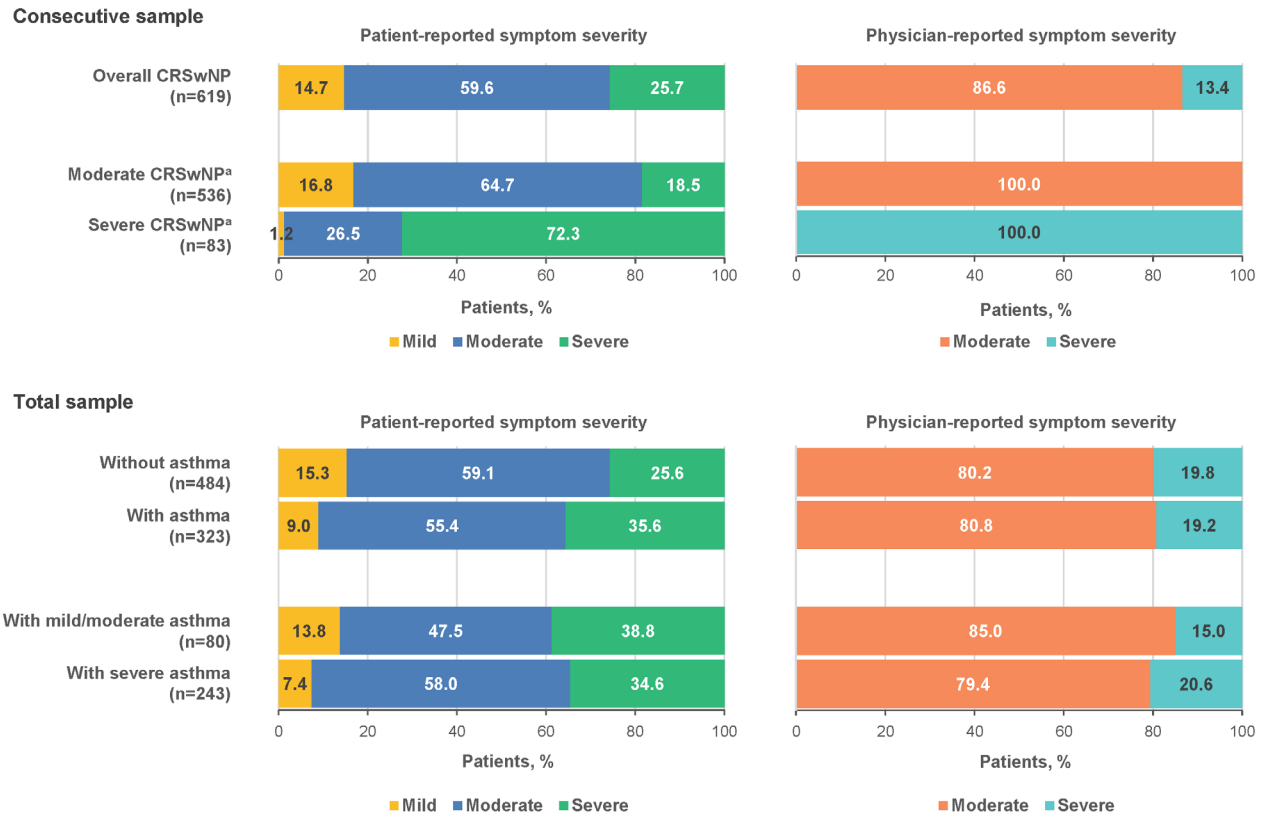

Figure 4. Overall severity of CRSwNP from matched patient/physician perspectives. [a] CRSwNP severity determined by physician for each patient based on physician's clinical expertise and provided guidance to follow the European Position Paper on Rhinosinusitis and Nasal Polyps guidelines [2,10] and NP size scoring systems. Abbreviations: CRSwNP, chronic rhinosinusitis with nasal polyposis; NP, nasal polyp.

vs. 94.7% of patients without asthma, and by 98.8% of patients with severe asthma vs. 90.1% with mild/moderate asthma. In comparison, symptoms of nasal blockage were identified by physicians in greater percentages of patients with vs. without comorbid asthma (90.2% vs. 87.4%), and in patients with severe vs. mild/moderate comorbid asthma (92.2% vs. 84.0%). In these subgroups of patients with known comorbid asthma status, a greater proportion of those with comorbid asthma reported their overall disease to be severe than those without asthma (35.6% vs. 25.6%; Figure 4).

Impact of symptoms on daily activities and work productivity

The impact level of CRSwNP symptoms on aspects of daily activities was assessed using data from all patient record forms filled out by physicians, resulting in approximately twice as many patients included for physician-reported data than for patient-reported data. Both patients and physicians reported a more severe impact of symptoms on daily activities, relationships, and work/education among individuals with severe CRSwNP than among those with moderate CRSwNP (Supplemental Figure 3). For example, the percentages of patients and physicians who noted the impact of symptoms on work/education to be severe were approximately 6 and 8 times higher among patients with severe CRSwNP than those with moderate CRSwNP (32.1% patients and 33.3% physicians vs. 4.2% patients and 5.4% physicians, respectively). Similarly, the severity of symptom impact on daily activities was greater among those with comorbid asthma than those without asthma (Supplemental Figure 4). This is illustrated by a greater percentage of patients and physicians listing a severe impact on work/education in 11.7% and 13.3% of patients with asthma compared with 7.5% and 9.6% of those without asthma, respectively (approximately 1.5 to 2 times greater percentages).

The patient-reported impact of CRSwNP symptoms on work productivity and activity was greater among patients with severe CRSwNP than among those with moderate disease and was also greater for those with asthma than for those without asthma (Supplemental Figure 5). The mean percentage of impairment while working affected by symptoms was 41.0% for those with severe CRSwNP vs. 27.9% for those with moderate CRSwNP; 35.6% vs. 27.0% in those with and without asthma; and 39.5% vs. 25.2% in those with severe and mild/moderate asthma.

Figure 5. Patient-reported burden of CRSwNP symptoms on overall health-related quality of life. [a] CRSwNP severity determined by physician for each patient based on physician's clinical expertise and provided guidance to follow the European Position Paper on Rhinosinusitis and Nasal Polyps guidelines [2,10] and NP size scoring systems. Gray line indicates SD. Abbreviations: CRSwNP, chronic rhinosinusitis with nasal polyposis; EQ-VAS, EuroQoL visual analogue scale; NP, nasal polyp; SNOT-22, 22-item Sino-Nasal Outcome Test.

Patient-reported burden of symptoms on HRQOL

Worse HRQOL scores (as observed by higher SNOT-22 total scores and lower EQ-VAS scores) were reported by patients with severe CRSwNP compared with moderate CRSwNP and by patients with comorbid asthma compared with patients without asthma (Figure 5). The mean SNOT-22 total score was approximately 1.5-fold higher, and the mean EQ-VAS score was approximately 1.2-fold lower for patients with severe vs. moderate CRSwNP, indicating a higher burden of CRSwNP symptoms on HRQOL. Among patients with confirmed asthma status, the mean SNOT-22 total score was greater and the mean EQ-VAS score was lower among those with comorbid asthma vs. those without asthma. Similar trends were observed when comparing patients with severe vs. mild/moderate asthma.

Discordance of patient- and physician-reported disease burden

In the matched analyses, a clear discordance was observed between reports of symptom prevalence and overall disease severity between physicians and patients across all subpopulations, with patients reporting both higher symptom prevalence and overall disease severity than physicians (Figures 2, 3, and 4; Supplemental Figures 1 and 2). Lower frequencies of symptoms were reported by physicians vs. patients for the most frequent nasal symptoms such as nasal blockage, need to blow nose, and runny nose, as well as across all the symptoms. Although there was an overall agreement between physicians and patients in the ranking of symptoms, the level of discordance appeared to be the greatest with non-nasal symptoms and impact of CRSwNP on HRQOL domains. For example, the difference between physicians and patients in reporting nasal blockage was 1.1-fold lower (87.8% vs. 95.1%) compared with 1.7-fold lower for decreased sense of smell/taste (45.5% vs. 75.8%), 2.6-fold lower for waking up tired (26.4% vs. 68.2%), 4.1-fold lower for reduced productivity (14.6% vs. 59.6%), 5-fold lower for dizziness (8.6% vs. 42.9%), and 6-fold lower for feeling embarrassed

(7.5% vs. 45.0%) (Figure 2).

The discordance between patients' and physicians' reports persisted in the analysis of the level of impact of CRSwNP symptoms on daily activities (Supplemental Figures 3 and 4). In these analyses, across patient populations and domains of daily activities, physicians consistently reported higher percentages of moderate level of impact than patients did, whereas patients reported higher percentages of severe or as-bad-as-can-be level of impact than physicians did.

Discussion

This study, which used physician and patient self-reported data collected in real-world clinical settings through validated questionnaires, demonstrated high CRSwNP disease burden and impact of symptoms on HRQOL throughout subpopulations of patients with moderate to severe CRSwNP. Patients with severe CRSwNP, comorbid asthma, and comorbid severe asthma reported higher symptom burden and greater impact on HRQOL compared with patients with moderate CRSwNP, CRSwNP without comorbid asthma, and CRSwNP with mild to moderate comorbid asthma. While there was some level of agreement between physician- and patient-reported prevalence of nasal clinical CRSwNP symptoms such as nasal blockage and need to blow nose, physicians generally underestimated the severity of all symptoms (clinical and non-clinical) and markedly underreported non-clinical symptoms or the level of impact of CRSwNP symptoms on patients' HRQOL. This may represent an unmet need of patients with CRSwNP. These discordances were consistent across all analysed subpopulations. This is the first study to compare patient- with physician-reported outcomes such as those measured by the SNOT-22. By providing physicians with the opportunity to report on a full range of patient symptoms, we identified specific unmet needs of potentially under-evaluated non-nasal–specific symptoms of patients with CRSwNP, which can help facilitate improved communication around patients' full range of NP symptoms and demonstrate the wider symptom burden that may remain underrecognized or underappreciated by physicians. These findings corroborate a recently published statement from the Patient Advisory Board of the European Forum for Research and Education in Allergy and Airways diseases (EUROFEA), in which interviews of European patients with CRSwNP brought to light the significant underestimation of the burden of this condition [17].

Although previous evaluations of CRSwNP symptom burden across disease severity categories are limited, they are consistent with our findings [7,18]. Our findings also confirmed those of previous studies that demonstrated a higher burden of CRSwNP symptoms on HRQOL and daily activities for patients with comorbid asthma [4,7]. Furthermore, in this study, patients with severe asthma per GINA criteria experienced a greater burden of CRSwNP symptoms than patients with asthma that was not severe. Research suggests that this may be due to the overlap in allergic phenotype between CRSwNP and asthma, involving T-helper type 2 lymphocytes and immunoglobulin E–mediated inflammation in both the upper and lower airways [4,19]. This results in more severe symptoms and higher symptomatic burden in patients with CRSwNP and asthma, with a cumulative negative impact on a patient's HRQOL.

Symptom impact on work productivity and activity impairment was highest for patients with severe CRSwNP. This is in line with findings from analyses that reported higher rates of absenteeism and lost productivity for patients with sinusitis and CRSwNP than for those without sinus problems, which also highlights the substantial economic burden of this condition to society [6,17,20–24].

One of this study's limitations was that the sample collected was not a true random sample of patients, potentially restricting the generalizability of our findings to that of the entire CRSwNP population. Although patient selection bias is possible, prospective consecutive sampling limits any bias that relates to physician pre-selection of individuals. This approach is contingent on the integrity of the participating physicians for recruiting consecutive patients, which cannot be verified. The physician-confirmed diagnosis and determination of moderate and severe CRSwNP may or may not have included diagnosis by endoscopy or another diagnostic technique. This is a common and accepted limitation of real-world data. However, guidance to physicians was given to follow the European Position Paper on Rhinosinusitis and Nasal Polyps guidelines and NP size scoring. Nonetheless, identification of target patient groups based on physicians' judgement rather than on a formal diagnostic checklist, was representative of physicians' real-world classification of patients. The inclusion of additional patients with repeat NPs and a history of sinonasal surgery increased the size of the severe CRSwNP population, which might also potentially be limited by a similar non-random selection bias toward more severe disease. Also, while minimal inclusion criteria governed the selection of the participating physicians, participation was influenced by willingness to complete the survey and by pragmatic geographical considerations such as a concentration of recruitment in urban areas.

Another bias may have been introduced from inherent differences between patients who agreed to complete their self-completion form and those who did not complete the form, which were excluded from the matched analyses. Still, the lack of significant differences between the demographics and clinical characteristics of patients with and without a self-completion form may strengthen our conclusions and improve the generali-

zability of the matched analyses.

Conclusions

Patients with moderate to severe CRSwNP reported a substantial symptom burden and a high impact on HRQOL, which is intensified for patients with severe CRSwNP and for those with comorbid asthma. Symptom severity and prevalence were underreported by physicians compared with patients' self-reports, including both clinical and non-clinical symptoms such as impact on HRQOL. Physicians also underestimated the impact level of CRSwNP symptoms on patients' daily activities. When assessing CRSwNP symptoms and HRQOL burden, a more patient-centric view should be taken. By stratifying participants into various subpopulations, we have identified a greater unmet need of underappreciated symptoms for patients with more severe NP symptoms, particularly for patients with comorbid asthma.

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Authorship contribution

SYC, MB, MScott, MSmall, SR, and BE: Study design, data analysis and interpretation, manuscript review and revision. LSWL: data analysis and interpretation, manuscript review and revision.

Ethics approval and consent to participate

The survey received ethical exemption determination by the Western institutional review board, a centralised international board for the United States (Study Number: #1-1090610-1), Europe, and Japan (Study Number: #1-1162676-1).

Consent for publication

Not applicable.

Conflict of interest

SYC and BE are employees of AstraZeneca and own stocks of AstraZeneca and other equities. MScott, MSmall, and LSWL are employees of Adelphi Real World. SR is a former employee of AstraZeneca. MB was an employee of AstraZeneca at the time of study.

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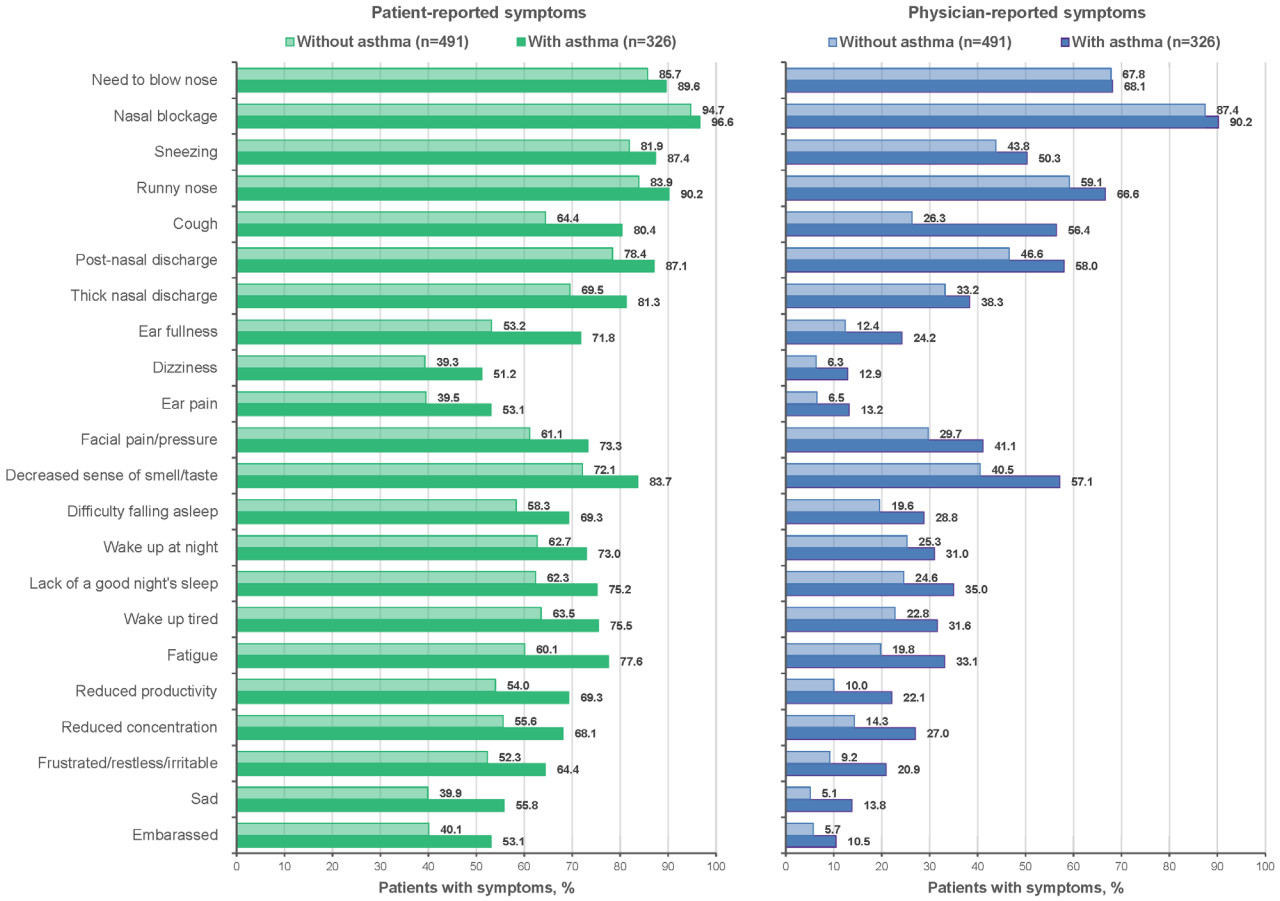
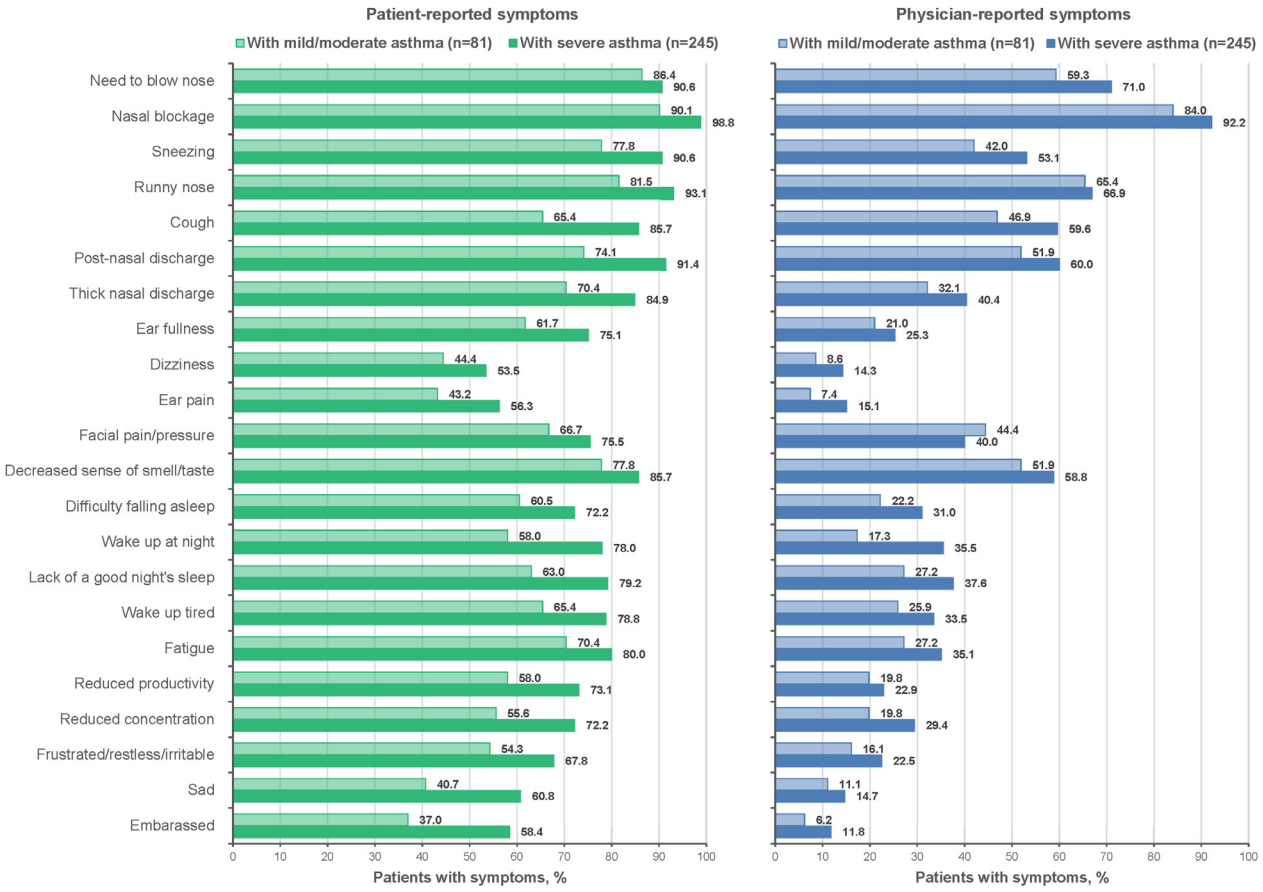
SUPPLEMENTAL DATA



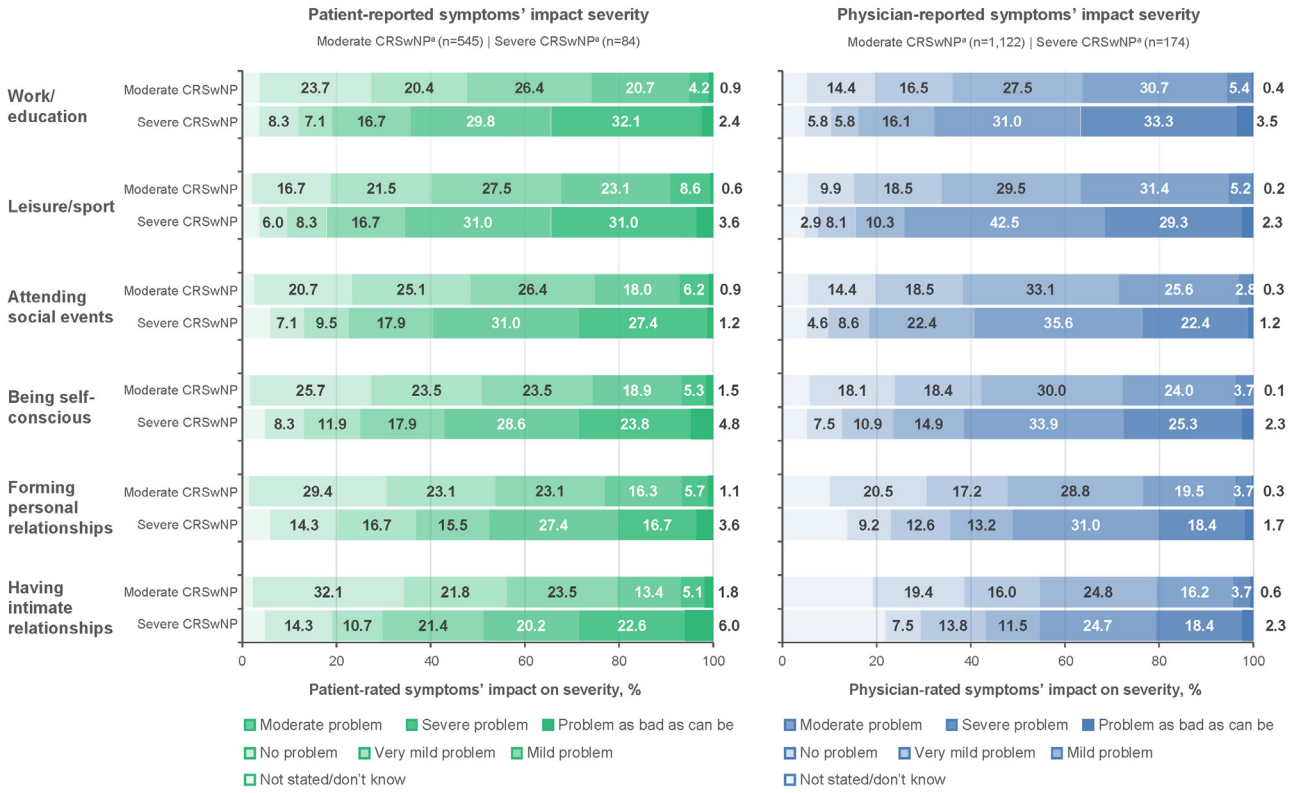
Supplemental Figure 1. Prevalence of reported CRSwNP symptoms from matched patient/physician perspectives by categories of asthma comorbidity (total sample with known asthma status).

Abbreviation: CRSwNP, chronic rhinosinusitis with nasal polyposis.



Supplemental Figure 2. Prevalence of reported CRSwNP symptoms from matched patient/physician perspectives by categories of comorbid asthma severity (total sample with comorbid asthma).

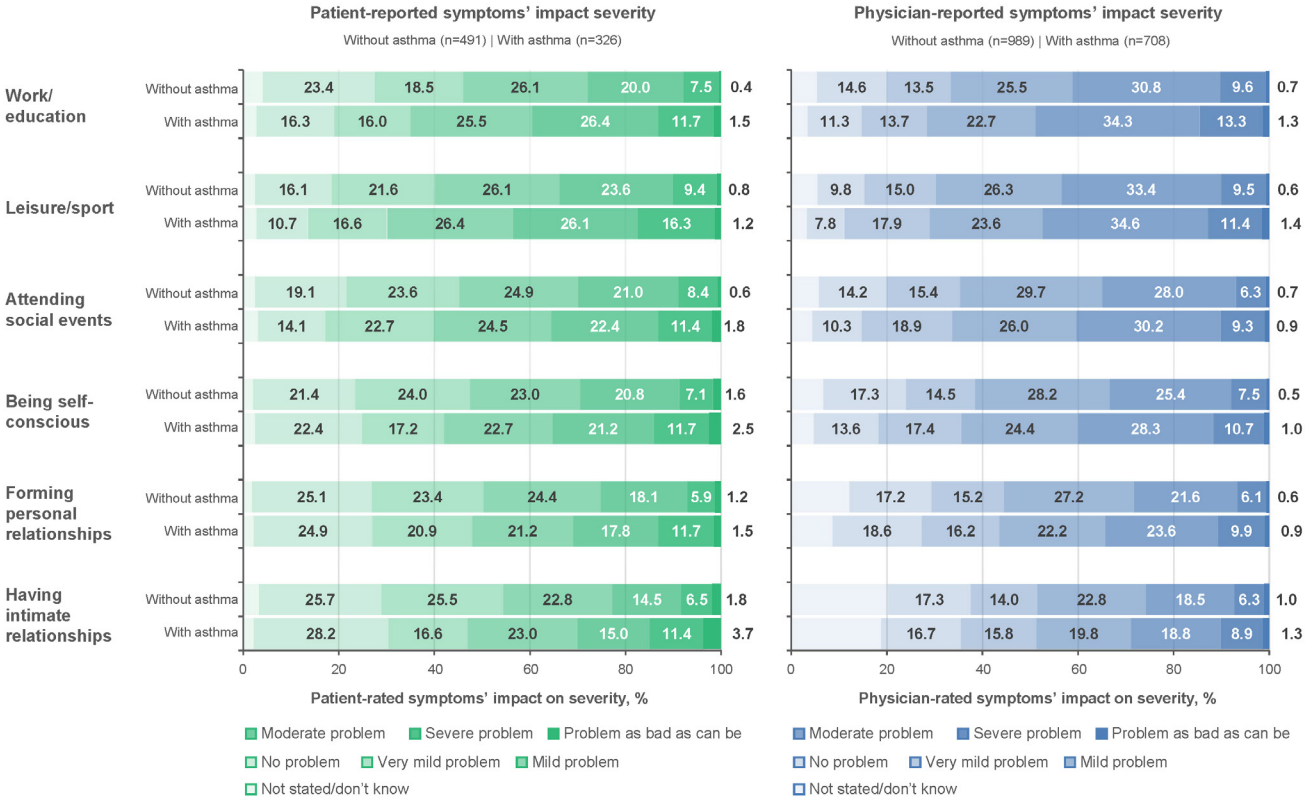
Abbreviation: CRSwNP, chronic rhinosinusitis with nasal polyposis.



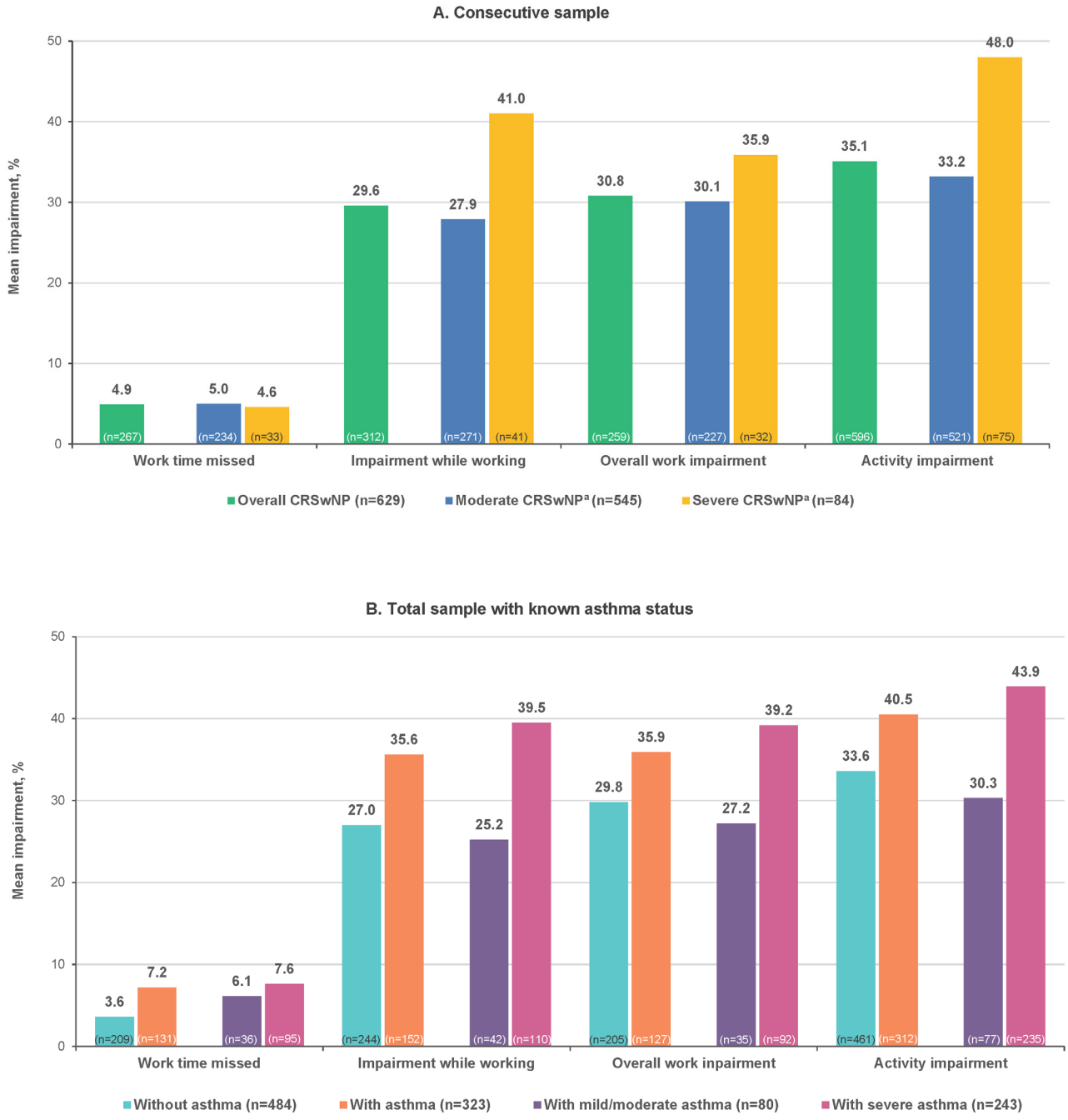
Supplemental Figure 3. Extent of CRSwNP symptoms' impact on daily activities and relationships by categories of CRSwNP severity (consecutive sample).

[a] CRSwNP severity determined by physician for each patient based on physician's clinical expertise and provided guidance to follow the European Position Paper on Rhinosinusitis and Nasal Polyps guidelines [2,10] and NP size scoring systems.

Abbreviations: CRSwNP, chronic rhinosinusitis with nasal polyposis; NP, nasal polyp.



Supplemental Figure 4. Extent of CRSwNP symptoms' impact on daily activities and relationships by categories of asthma comorbidity (total sample with known asthma status). [a] CRSwNP severity determined by physician for each patient based on physician's clinical expertise and provided guidance to follow the European Position Paper on Rhinosinusitis and Nasal Polyps guidelines [2,10] and NP size scoring systems.
Abbreviations: CRSwNP, chronic rhinosinusitis with nasal polyposis; NP, nasal polyp.



Supplemental Figure 5. Patient-reported burden of CRSwNP symptoms on work productivity and activity impairment, (A) by categories of CRSwNP severity (consecutive sample) and (B) by categories of asthma comorbidity (total sample with known asthma status and asthma severity). [a] CRSwNP severity determined by physician for each patient based on physician's clinical expertise and provided guidance to follow the European Position Paper on Rhinosinusitis and Nasal Polyps guidelines [2,10] and NP size scoring systems.

Abbreviations: CRSwNP, chronic rhinosinusitis with nasal polyposis; NP, nasal polyp.

Supplemental Table 1. Sensitivity analysis of matched patient/physician reports.

	Without completed PSC (n=667)	With completed PSC (n=629)	p value
Age, mean (SD), y	46.5 (16.6)	47.3 (15.2)	0.376[a]
Male sex, n (%)	398 (59.7)	374 (59.5)	0.955[b]
BMI, mean (SD)	(n=666) 25.4 (4.9)	(n=626) 25.4 (4.2)	0.999[a]
Race/ethnicity, n (%)			0.012[c]
White/Caucasian	453 (67.9)	466 (74.1)	
African American (US)	29 (4.4)	10 (1.6)	
Native American (US)	1 (0.2)	0 (0.0)	
Asian-Indian subcontinent	12 (1.8)	4 (0.6)	
Asian, other	7 (1.2)	4 (0.6)	
Chinese	4 (0.6)	1 (0.2)	
Hispanic/Latino	16 (2.4)	16 (2.5)	
Middle Eastern	14 (2.1)	5 (0.8)	
Mixed race	10 (1.5)	4 (0.6)	
Afro-Caribbean (Europe)	8 (1.2)	6 (1.0)	
Japanese	112 (16.8)	113 (18.0)	
Other	1 (0.2)	0 (0.0)	
Tobacco smoking status, n (%)	(n=579)	(n=585)	0.127[c]
Current	87 (15.0)	93 (15.9)	
Former	123 (21.2)	151 (25.8)	
Never	369 (63.7)	341 (58.3)	
Comorbid condition,[d] n (%)			
Anxiety	44 (6.6)	35 (5.6)	0.486[b]
Allergic rhinitis	318 (47.7)	313 (49.8)	0.470[b]
Asthma	266 (39.9)	249 (39.6)	0.955[b]
Atopic dermatitis	46 (6.9)	48 (7.6)	0.669[b]
COPD	43 (6.5)	43 (6.8)	0.824[b]
Depression	42 (6.3)	22 (3.5)	0.021[b]
Elevated cholesterol/hyperlipidaemia	61 (9.2)	52 (8.3)	0.623[b]
Gastroesophageal reflux disease	45 (6.8)	46 (7.3)	0.745[b]
Hypertension	119 (17.8)	120 (19.1)	0.568[b]
Obesity	41 (6.2)	36 (5.7)	0.814[b]
Sleep apnoea	39 (5.9)	43 (6.8)	0.495[b]
CCI,[e] mean (SD)	0.18 (0.61)	0.13 (0.50)	0.111
Physician-perceived severity, n (%)			1.000[b]
Moderate	577 (86.5)	545 (86.7)	
Severe	90 (13.5)	84 (13.4)	
NP score			0.046[f]
Mean (SD)	3.4 (1.9)	3.6 (1.9)	
Median (IQR)	4.0 (2.0–4.0)	4.0 (2.0–5.0)	

[a] *t*-test. [b] Fisher's exact test. [c] Chi-square test. [d] Comorbid conditions related to CRSwNP and reported in >5% of patients. [e] The CCI is calculated based on the presence of select comorbidities. [f] Mann-Whitney test.

Abbreviations: BMI, body mass index; CCI, Charlson comorbidity index; COPD, chronic obstructive pulmonary disease; CRSwNP, chronic rhinosinusitis with nasal polyposis; IQR, interquartile range; NP, nasal polyp; PSC, patient self-completion forms.