Aeroallergen sensitization influences quality of life and comorbidities in patients with nasal polyposis

Ignacio Dávila, M.D., Ph.D.,¹ Carmen Rondón, M.D., Ph.D.,² Ana Navarro, M.D., Ph.D.,³ Encarnación Antón, M.D.,⁴ Carlos Colás, M.D., Ph.D.,⁵ María Teresa Dordal, M.D.,⁶ María Dolores Ibáñez, M.D., Ph.D.,⁷ Beatriz Fernández-Parra, M.D.,⁸ Magdalena Lluch-Bernal, M.D.,⁹ Víctor Matheu, M.D., Ph.D.,¹⁰ Javier Montoro, M.D.,¹¹ María Cesárea Sánchez, M.D., Ph.D.,¹² and Antonio Valero, M.D., Ph.D.¹³

ABSTRACT

Background: Nasal polyposis (NP) is a chronic inflammatory disease of unknown etiology that impairs quality of life (QoL). The role of atopy in NP is not established. The aim of this study was to describe the clinical characteristics and QoL in a broad sample of patients with NP and to evaluate the influence of allergy on this disease.

Methods: A multicenter, observational, cross-sectional study was conducted in 67 allergy units in Spain. NP and nonsteroidal anti-inflammatory drug (NSAID) hypersensitivity were diagnosed following EP³OS guidelines. Rhinitis and asthma were classified following Allergic Rhinitis and Its Impact on Asthma and the Global Initiative for Asthma guidelines, respectively. Skin tests with a battery of aeroallergens were performed on all patients. A visual analog scale (VAS) and Short-Form 12 (SF-12) and 31-item Rhinosinusitis Outcome Measure (RSOM 31) questionnaires were completed by all the patients.

Results: Of the 671 patients included, 611 were evaluable. Mean age was 46 years and 50% of patients were men. Also, 50% were atopic. Asthma was present in 66% of patients and NSAID hypersensitivity was present in 26%. The most frequent symptoms were nasal congestion and rhinorrhea. Mean value of VAS was 58.6. Global health and bodily pain were the items most frequently identified in the SF-12 questionnaire and nasal and ocular symptoms in the RSOM-31 questionnaire. There was a good correlation between VAS score and QoL ($p < 0.0001$). Rhinitis was more severe in nonallergic patients. Asthma was more frequent in atopic patients, whereas ASA triad was more frequent in nonatopic patients. Atopic patients showed higher VAS scores and worse QoL.

Conclusion: Atopic NP patients showed worse QoL, higher incidence of asthma and a less severe form of rhinitis than non-atopic patients.

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Nasal polyposis (NP) is a chronic inflammatory disease with an estimated prevalence of between 1 and 4.5% in adults and 0.1% in children.^{1,2} It is agreed that NP is a subgroup within chronic rhinosinusitis (CRS).³

The etiology of NP is unknown. To date, NP has been related to chronic inflammation, mucin expression, biofilms, *Staphylococcus aureus* enterotoxins, or oxidative stress.^{2–6} Moreover, some studies have pointed to an underlying genetic predisposition.⁵ In addition, it is not clear whether allergy is implicated in the development of NP.⁷ On the one hand the frequency of NP in patients with allergic rhinitis ranges between 0.5 and 4.5%.^{8,9} On the other hand, several studies have shown an increased prevalence of positive skin-prick tests among patients with NP.¹⁰

Quality of life (QoL) can be significantly impaired in patients with NP. Radenne *et al.*¹¹ and Alobid *et al.*¹² measured the QoL in patients

with NP using the Short Form 36 (SF-36) questionnaire. Both studies showed significant differences between healthy subjects and patients with NP in all the SF-36 domains, except for physical functioning in Alobid *et al.*¹² Moreover, they also found that patients with NP had lower scores in the mental score than in the physical score, which suggests that NP has a greater impact on mental health than on physical health.¹¹ NP also has an impact on other aspects of patients' lives and has been found to be associated with erectile dysfunction.¹³

In 2007, the updated consensus document EP³OS was published.³ New diagnostic and therapeutic regimens were suggested based on new data available on NP. In addition, clear epidemiological diagnostic criteria were defined. Therefore, the large epidemiological studies on NP^{2,8,14,15} performed before 2007 do not take into account the new EP³OS 2007 diagnostic criteria.

In the present study we aimed to evaluate the clinical characteristics of NP diagnosed following EP³OS guidelines, its repercussion on QoL, and the possible influence of allergy on NP.

METHODS

A multicenter, observational, cross-sectional study was conducted in 67 allergy units in Spain between June 2008 and September 2009. The protocol of the study was written according to the principles of the Declaration of Helsinki and was approved by the independent Ethics Committee of the Carlos Haya Hospital (Málaga, Spain).

Patients

Eligible patients were adults with NP who signed specific written informed consent. The diagnostic criteria for NP were those established in the EP³OS guidelines.³ Patients with nasal polyps of other etiology were excluded.

Clinical data were obtained from patient interviews at the study visit and from patients' medical records. Patients were enrolled consecutively as they attended the allergy clinics. Each allergy clinic should include 10 patients.

From the ¹Allergy Service, University Hospital of Salamanca, Spain, ²Allergy Service, Carlos Haya Hospital, Málaga, Spain, ³UGC Intercentros Valme-Rocio de Alergología, Hospital El Tomillar, Sevilla, Spain, ⁴Allergy Service, University Hospital Marqués de Valdecilla, Santander, Spain, ⁵Allergy Service, Hospital Clínico-Instituto de Investigación Sanitaria Aragón, Zaragoza, Spain, ⁶Allergy Service, Hospital Municipal de Badalona, Badalona, Spain, ⁷Allergy Service, Hospital Infantil Universitario Niño Jesús, Madrid, Spain, ⁸Allergy Service, Hospital El Bierzo, Ponferrada, León, Spain, ⁹Allergy Service, Hospital Virgen del Valle, Toledo, Spain, ¹⁰Allergy Service, Hospital del Tórax (Ofra), Complejo Hospitalario Universitario NSC, Unidad de Investigación, Hospital Universitario NS Candelaria, Tenerife, Spain, ¹¹Allergy Unit, Hospital Universitario Arnau de Vilanova, Valencia, Spain, ¹²Allergy Unit, CE Virgen de la Cinta, Hospital Juan Ramón Jiménez, Huelva, Spain, ¹³Allergy Unit, Servei de Pneumologia i Alergia Respiratòria, Hospital Clínic, Barcelona, Spain, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Centro de Investigación Biomédica en red en Enfermedades Respiratorias (CIBERES) Spain

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Address correspondence and reprint requests to Ignacio Dávila, M.D., Ph.D., Servicio de Alergia, Hospital Universitario de Salamanca, Planta Baja del Antiguo Hospital Materno Infantil, Paseo de San Vicente 58-182, 37007 Salamanca, Spain

E-mail address: idg@usal.es

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Study Assessments

The objective of the study assessments was to evaluate the clinical characteristics of NP and associated symptoms and diseases and to evaluate the QoL and the influence of allergy on NP. Intensity of nasal polyp symptoms was assessed by a 100-mm visual analog scale (VAS) ranging from 0 (no symptoms) to 100 (maximum symptom intensity). Data on comorbidities were also collected. Rhinitis was classified following Allergic Rhinitis and Its Impact on Asthma guidelines.¹⁵ Asthma was classified following Global Initiative for Asthma guidelines (www.ginasthma.com). Atopy was defined by the existence of at least one positive skin test to a common local battery of aeroallergens. Skin-prick tests were performed with locally adapted batteries of aeroallergens that at least should include house-dust mites, molds, pollens, epithelia, and cockroach. Nonsteroidal anti-inflammatory drug NSAID hypersensitivity diagnostic criteria were those specified in the EPO³S document.³

QoL was assessed by the Spanish-validated 2nd Version of the SF-12 Health Survey^{17,18} and the 31-item Rhinosinusitis Outcome Measure (RSOM-31) questionnaire.¹⁹ The SF-12 is a reduced version of the SF-36 Health Survey recommended for sample sizes of >500 patients. It consists of 12 self-administered questions evaluated by Likert-type scales, which can be answered in <2 minutes. The 2nd Version of the SF-12 allows two summary scores (physical composite score [PSC] and mental composite score [MCS]) to be obtained as well as the scores for the eight dimensions of the SF-36. The RSOM-31¹⁹ is a self-administered questionnaire specific for rhinosinusitis, which can be answered in ~20 minutes. The RSOM-31 consists of 31 items classified into seven domains (nasal, eye, ear, sleep, general, emotional, and functional). Each item has two evaluations, on magnitude and on importance to the patient. The patient's impact score for each symptom is obtained by the product of the magnitude and importance scores and is unique and specific for each item. In this questionnaire, the higher the score, the lower the QoL. Because there is no a specific validated QoL test for NP, we decided to use the RSOM-31 questionnaire in our study.

Statistical Analysis

A sample size of 600 patients with NP was estimated to achieve a 4% precision with a 95% confidence interval, considering a 5% loss of evaluable patients. The statistical analysis was performed with the Version 9.2 of SAS (SAS Institute, Inc., Cary, NC). A value of *p* < 0.05 was considered significant.

Qualitative variables were described using frequencies and quantitative variables by means of centralization and dispersion measures. For comparisons, a chi-squared test or a Fisher's exact test for categorical variables or a Student's *t*-test or a Kruskal-Wallis test for continuous variables were used. For comparisons with three or more categories an ANOVA test was implemented.

RESULTS

Baseline Demographics and Clinical Characteristics

Overall, 671 patients were recruited by 67 participating centers. Of these, 611 (91%) were evaluable, and 60 (9%) were excluded for not fulfilling inclusion criteria. Table 1 shows patients' baseline demographic and clinical characteristics. Briefly, the mean age of patients was 46 years and the mean age at onset of symptoms was 30 years. Patients had suffered from NP for a mean of 90 months and rhinitis for a mean of 133 months. Asthma was present in 397 patients with a mean time of progression of 52 months. NSAID hypersensitivity was present in 159 patients (26.0%) with a mean progression time of 115.6 months (*n* = 139). Two hundred twenty-five patients (36.8%) had undergone polypectomy with a mean of 1.7 ± 2.22 polypectomies per patient. The mean value of VAS was 58.6. Sixty-seven patients (11%)

Table 1 Baseline demographic and clinical data (*n* = 611)

Age (yr), mean (SD)	46.09 (13.48)
Sex, male, <i>n</i> (%)	303 (49.8)
Ethnic group, <i>n</i> (%)	
White	603 (98.7)
South-American or African	8 (1.3)
Age of first symptoms (yr), mean (SD)	30.07 (8.51)
Smoking, <i>n</i> (%)	
Nonsmoker	423 (69.9)
Exsmoker (>5 yr)	114 (18.8)
Smoker	68 (11.2)
Family history of nasal polyposis, <i>n</i> (%)	67 (11.0)
Number of polypectomies, mean (SD)	1.76 (2.22)

Table 2 Nasal and associated symptoms in patients with NP*

Main Nasal and Accompanying Symptoms	<i>n</i> (%)
Nasal congestion	537 (87.9)
Rhinorrhea	489 (80)
Reduction/loss of smell	448 (73.3)
Sneezing	444 (72.7)
Nasal itching	345 (56.5)
Ocular symptoms	213 (34.9)
Headache	251 (41.1)
Snoring	202 (33.1)
Sleep disorders	168 (27.5)
Sensation of ear blockage	125 (20.5)
Recurrent pharyngitis	72 (11.8)
Asthenia	67 (11.0)
Ear pain	38 (6.2)
Dizziness	33 (5.4)

*Frequency of ≥5%.
NP = nasal polyposis.

had a family history of NP, generally from the father or siblings (39% each).

The nasal and associated symptoms are shown in Table 2. Nasal congestion, rhinorrhea, and reduction/loss of smell were the most frequent nasal complaints. Eye symptoms were present in 34.9% of patients. Other associated complaints were headache (mainly frontomaxillary or described as a heavy feeling in the head), snoring, sleep disturbances, a sense of ear blockage, and asthenia.

The final diagnoses of patients (*n* = 602) were NP with asthma (39.7%), NP (31.1%), ASA triad (26.2%), and NP with NSAID hypersensitivity (3%). VAS values were not significantly different between patients with NP with or without asthma.

Quality of Life

QoL results, as measured by the SF-12 and RSOM-31 questionnaires, are shown in Table 3. For both questionnaires, patients with asthma and/or NSAID hypersensitivity showed a significantly impaired QoL when compared with those patients that exclusively had NP (Table 4). Briefly, overall health and bodily pain were the items most frequently identified in the SF-12 questionnaire and nasal symptoms and ocular symptoms in the RSOM-31 questionnaire.

There was a good correlation between VAS score and QoL as measured by SF-12 and RSOM-31 (*p* = 0.0001 for both).

Influence of Allergen Sensitization

One-half of patients were atopic (50%; *n* = 596). Main sensitizations were house-dust mites (66.4% of allergic patients), pollens (69.1%), animal dander (35.6%), and molds (14.09%). Food allergy was present in 3.8% of patients.

Table 3 Quality of life scores

	<i>n</i>	Mean (SD)
SF-12		
Physical composite score	571	47.69 (7.40)
Mental composite score	571	50.60 (5.91)
Physical functioning	585	68.55 (30.20)
Physical role	598	74.50 (24.76)
Bodily pain	603	78.57 (26.49)
General health	604	41.76 (18.98)
Vitality	596	37.42 (25.04)
Social functioning	599	80.84 (25.15)
Emotional role	597	80.07 (23.70)
Mental health	595	51.30 (14.17)
RSOM-31		
Nasal symptoms	534	7.53 (4.33)
Eye symptoms	537	3.14 (4.59)
Sleep symptoms	524	5.95 (5.93)
Ear symptoms	499	1.97 (3.23)
General symptoms	367	4.36 (4.28)
Practical problems	516	6.82 (5.53)
Emotional consequences	528	4.93 (5.49)
Total score	299	3.53 (2.98)

SF-12 = Short Form 12; RSOM-31 = 31-item Rhinosinusitis Outcome Measure.

When we compared atopic and nonatopic patients, a statistically significant difference ($p = 0.0009$) was observed in the type and severity of associated rhinitis, with persistent moderate or severe rhinitis being more frequent in nonatopic NP patients (data not shown). In Table 5 the main significant differences are listed. Asthma was significantly more frequent in atopic patients, whereas ASA triad was more frequent in nonatopic patients ($p = 0.0001$). In addition, 59.6% of patients with NP and asthma had a family history of allergy, whereas this percentage was 41.7% in patients with only NP and 42.1% in patients with ASA triad ($p = 0.0003$; data not shown). The VAS score was significantly higher in atopic patients with NP (60.81 versus 53.32; $p = 0.023$). No significant differences were observed in the number of polypectomies between atopic and nonatopic NP patients. There were no significant differences in QoL between atopic and nonatopic NP patients in the SF-12 questionnaire but in the RSOM-31 questionnaire atopic NP patients showed worse QoL (Table 6).

DISCUSSION

The present study, involving 611 evaluable patients, offers valuable insight into the clinical characteristics of NP and associated diseases and aeroallergen sensitization. To the best of our knowledge, this is the largest study centered on patients with NP and the first to select patients according to the new EPOS 2007 diagnostic criteria.

In our population, mean patient age was 46 years. This is in accordance with previous studies performed both in Spain^{10,20} and in other countries.² Although NP is two- to fourfold more prevalent in men than in women,^{1,10,15,20} only one-half of the patients recruited in this study were men. Nevertheless, this is in line with a large, population-based epidemiological study performed in France, where 45% of patients with NP were men² as well as with the study of Settignano *et al.*²¹ that described a similar percentage of men and women. In addition, this gender distribution could have been influenced by the fact that more women than men attend allergy consultations in Spain for rhinitis²² and asthma,²³ the main comorbidities associated with NP.

The main symptoms associated with NP were nasal congestion, rhinorrhea, and abnormalities of sense of smell, followed by sneezing.

Nasal itching and ocular symptoms were less frequent. In the larger series, nasal congestion was the most frequent symptom, ranging 30.8 to 88.5%,^{15,20} although in some the most frequent symptom was rhinorrhea.^{15,24} Although smell disorders have been considered more prevalent in patients with NP than in other CRS patients³, it is not usually described as being as frequent as nasal congestion or rhinorrhea.^{15,20,24} In addition, in our study, the main associated complaints were headache, snoring, and sleep disturbances.

The most frequent comorbidities were asthma (65%) and NSAID hypersensitivity (26.2%). The percentage of asthma in patients with NP is similar to that found in other studies.^{10,7} Similarly, the percentage of NSAID hypersensitivity is similar to that described previously in the main series: 31% in the study of Crampette *et al.*,²⁵ 20.3% in the study of Klossek *et al.*,² and 26.7% in that of Toledano *et al.*²⁰

Several studies have pointed to an influence of genetic factors on NP. Family-based studies have shown familial aggregation of NP^{5,26} and several polymorphisms have been associated with NP.^{27,28} In addition, Rugina *et al.*¹⁵ found that 52.66% of 224 patients with NP had positive family history of NP in the last three generations. In contrast, Greisner *et al.*²⁹ only found a 14% positive family history in 50 patients with NP and Toledano *et al.*²⁰ found positive first-degree family history in 20% of NP patients. The figures in the present study are similar: only 11% of patients had a positive family of NP, even if they were specifically asked about two generations. Nevertheless, because no clinical evaluation was performed on the relatives this percentage could be underestimated.

Few data have been published regarding QoL in NP, and most of these have evaluated patients with CRS. These studies can be divided according to whether they used a generic (mainly, SF-36 health survey) or specific questionnaire (mainly, RSOM-31 and 20-item Sino-Nasal Outcome Test). We used a generic questionnaire, the SF-12, and a specific questionnaire, the RSOM-31. Radenne *et al.*¹¹ and Alobid *et al.*¹² measured the QoL in patients with NP using the SF-36 questionnaire. Both studies showed significant differences between healthy subjects and patients with NP in all the SF-36 domains, except for physical functioning in Alobid *et al.*¹² Moreover, they also found that patients with NP had lower scores in the MCS than in the PSC, which suggests that NP has a greater impact on mental health than on physical health.^{11,12} Our results from the SF-12 questionnaire showed similar scores between MCS and PSC. In fact, the MCS scores were slightly higher in MCS (50.6 versus 47.69), although they were lower than the values found in the Spanish general population (MCS = 79.7; PCS = 78.8).¹²

It has been shown that patients with NP have lower scores in SF-36 than patients with coronary artery disease, asthma, and chronic obstructive pulmonary disease.^{30,31} Hissaria *et al.*³² published the only study focusing specifically on NP using a modified RSOM-31 questionnaire. At baseline, they found average scores of 2.2 and 1.87 in patients to be treated with placebo and with corticosteroids, respectively. These results are lower than those found in our study, in which patients had an RSOM-31 average score of 3.53. However, such differences could be caused by the fact that Hissaria *et al.*³² used a modified questionnaire that only included severity scores. Unfortunately, the authors did not report any other RSOM-31 evaluations at baseline.

We observed a good correlation between VAS score and QoL as measured by SF-12 and RSOM-31 questionnaires. This is in agreement with data from Zheng *et al.* who found that the 20-item Sino-Nasal Outcome Test, SF-36, and VAS correlated well with each other.³³

In our study, we observed that patients with NP and asthma and/or NSAID hypersensitivity had an impaired QoL compared with patients that only suffered from NP without comorbidities. Alobid *et al.*³⁴ reported a similar finding.

The role of allergy in the pathogenesis of NP is unknown. It has been described that between 10 and 64% of patients with NP have allergy¹. In our sample, 50% of patients had allergy, which is slightly less than the figure of another study performed in Spain by Muñoz del

Table 4 Evaluation of quality of life according to final patient diagnosis

Variable		Total	Nasal Polyps	Nasal Polyps and Asthma	ASA Triad	p Value*
SF-12v2 value physical component	<i>n</i>	550	176	227	147	<0.0001
	Mean (SD)	39.53 (8.41)	42.67 (7.00)	38.56 (8.54)	37.27 (8.72)	
	Median	40.9	43.6	39.5	37.6	
	P25; P75	34.2; 46.1	39.1; 47.3	33.4; 45.7	30.5; 43.9	
	Missing	34	11	12	11	
SF-12v2 value mental component	<i>n</i>	550	176	227	147	0.0031
	Mean (SD)	46.14 (9.04)	47.96 (7.86)	45.68 (9.09)	44.69 (9.94)	
	Median	48.1	48.9	48.0	46.2	
	P25; P75	41.1; 52.1	46.0; 52.2	39.1; 52.1	38.0; 52.0	
	Missing	34	11	12	11	
Severity RSOM-31	<i>n</i>	569	183	231	155	0.0009
	Mean (SD)	4.81 (3.38)	4.05 (3.27)	5.21 (3.37)	5.13 (3.39)	
	Median	4.0	3.1	4.4	4.5	
	P25; P75	2.1; 6.8	1.5; 5.6	2.6; 7.3	2.5; 7.2	
	Missing	15	4	8	3	

*Student's *T*.

P25; P75 = 25-75 percentiles; SF-12 = Short Form 12; RSOM-31 = 31-item Rhinosinusitis Outcome Measure.

Table 5 Analysis of the influence of allergy on NP

Variable		Total	Atopic NP Patients	Nonatopic NP Patients	p Value*
Type of NP					
Total		602 (100.0%)	331 (100.0%)	271 (100.0%)	<0.0001
NP		187 (31.1%)	97 (29.3%)	90 (33.2%)	
NP with NSAID hypersensitivity		18 (3.0%)	5 (1.5%)	13 (4.8%)	
NP with asthma		239 (39.7%)	159 (48.0%)	80 (29.5%)	
ASA triad		158 (26.2%)	70 (21.1%)	88 (32.5%)	
Total		602 (100.0%)	331 (100.0%)	271 (100.0%)	<0.0001
Polypectomies					
Total		611 (100.0%)	338 (100.0%)	273 (100.0%)	0.5585
Yes		225 (36.8%)	121 (35.8%)	104 (38.1%)	
No		386 (63.2%)	217 (64.2%)	169 (61.9%)	
Presence of asthma					
Total		611 (100.0%)	338 (100.0%)	273 (100.0%)	0.0372
Yes		377 (61.7%)	221 (65.4%)	156 (57.1%)	
No		234 (38.3%)	117 (34.6%)	117 (42.9%)	

*Student's *t*-test.

NP = nasal polyposis; NSAID = nonsteroidal anti-inflammatory drug.

Castillo *et al.*¹⁰ who found positive skin-prick tests in 63.2% of 190 patients with NP. Other studies have found percentages of positive skin tests between 16 and 35%.^{2,7,25} These differences could depend in part on what specialists have recruited patients. Generally speaking, when patients came from allergy services the figures tend to be higher.^{21,35,36} In addition, atopic and nonatopic NP patients had differences in severity of the diseases and associated comorbidities. Thus, atopic patients had asthma more frequently, whereas the ASA triad was significantly more frequent among nonatopic patients. In a study evaluating the influence of allergy on NP, Bonfils *et al.*⁷ found no difference in the mean of nasal symptoms between allergic and nonallergic patients with NP. Nevertheless, they found an increase in the prevalence of asthma in the allergic group, which is in agreement with our results. Also, nonatopic patients had moderate or severe persistent rhinitis more frequently. Atopic patients scored higher on VAS and complained of lower QoL. Recently, Kirtsreesakul *et al.*³⁷ have described an increase in mucociliary clearance time in patients with allergic rhinitis compared with patients with nonallergic rhinitis who also had higher total nasal symptom scores and lower peak

expiratory flow indices. This could explain the higher score in VAS and the lower score on QoL scales. Similarly, in a study comparing QoL between atopic and nonatopic NP patients, Alobid *et al.*³⁸ showed a significant reduction in QoL in atopic NP patients compared with nonatopic NP patients.

In conclusion, we present the results of the largest epidemiological study on NP, providing a picture of the demographic parameters, clinical characteristics, comorbidities, and QoL. Atopic NP patients had several differences compared with nonatopic patients, showing less severe forms of rhinitis but higher incidence of asthma. In addition, atopic NP patients showed a significantly worse QoL than nonatopic NP patients.

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Table 6 Differences in quality of life between atopic and nonatopic NP patients

Variable	Total	Atopic NP Patients	Nonatopic NP Patients	p Value*
SF-12v2 value physical component				
n	545	266	279	
Media (SD)	39.73 (8.46)	40.12 (8.19)	39.36 (8.71)	0.2938
Median	41.4	41.5	40.6	
P25; P75	34.4; 46.2	35.2; 46.4	32.4; 46.2	
n Missing	36	17	19	
SF-12v2 value mental component				
n	545	266	279	
Media (SD)	46.10 (9.04)	45.52 (9.04)	46.66 (9.03)	0.1423
Median	48.2	47.7	48.8	
P25; P75	41.2; 52.1	40.2; 51.7	41.6; 52.2	
n Missing	36	17	19	
Severity RSOM-31				
n	565	274	291	
Media (SD)	4.77 (3.36)	5.12 (3.50)	4.43 (3.20)	0.0149
Median	4.0	4.4	3.7	
P25; P75	2.1; 6.8	2.5; 7.2	1.9; 6.7	
n Missing	16	9	7	

*Student's t-test.

P25; P75 = 25-75 percentiles; NP = nasal polypsis; SF-12 = Short Form 12; RSOM-31 = 31-item Rhinosinusitis Outcome Measure.

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