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Prevalence and Symptom Burden of Nasal Polyps in a Large Austrian Population

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AUTHOR CONTRIBUTION STATEMENT

VN had the initial idea for the retrospective analysis and RK performed all data collection. NJC, RK, SVM, JED and VN interpreted the data and designed the figures. All authors wrote and critically revised the manuscript together. RR advised on and performed key statistical analyses.

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ABSTRACT

Background: Although chronic rhinosinusitis with nasal polyps (CRSwNP) is a common inflammatory condition with significant morbidity and financial cost, information regarding prevalence and disease burden of this condition is scarce.

Objective: In this study we determined nasal polyp prevalence, polyp grade, concomitant disease, and symptom burden in > 10,000 central European subjects.

Methods: In this retrospective, cross-sectional study, 10,259 patients who had undergone routine examination of their nose by nasal endoscopy during a visit at a publicly accessible ENT outpatient facility in Vienna were included. Patient details including presenting complaint, nasal symptoms, polyp score, age, gender, treatment, asthma and allergic status were extracted retrospectively. A detailed questionnaire including history of nasal symptoms, SNOT-20 GAV, and VAS was available for 101 patients with nasal polyps.

Results: Nasal polyps were detected in 189 (1.84%) of the 10,259 patients. The calculated prevalence of polyps in Austria, adjusted for age and gender, was 1.95%. The average TPS was 3.4, 72.5% had a TPS of ≤ 4 , with males and asthmatics having significantly larger polyps. Questionnaire analysis revealed that 67% suffered from a low symptom burden of ≤ 36 . According to current EPOS guidelines, 6% of polyp patients fulfilled and another 8% potentially fulfil the eligibility criteria for biological therapy.

Conclusion: Nasal polyp prevalence was calculated to be 1.95% of the Austrian population. Large polyps (TPS>4) were found in 25%, 33% suffered from a high nasal symptom burden, and between 6 to 14% of polyp patients would be eligible for biological therapy according to EPOS guidelines.

Highlights Box bulleted answers:

- What is already known about this topic?

Previous prevalence studies estimated the frequency of nasal polyps between 2-4%. However they mainly relied on patient reporting, record keeping or questionnaires to determine the presence of nasal polyps and did not assess symptom burden.

- What does this article add to our knowledge?

The prevalence of nasal polyposis assessed in >10,000 Europeans using nasal endoscopy is 1.95%. Additionally detailed knowledge on polyp burden, presence of symptoms of chronic rhinosinusitis and impairment of quality of life in this population.

- How does this study impact current management guidelines

Our estimations on eligibility of nasal polyp patients for biological therapy will impact infrastructure planning across Europe.

Key words: chronic rhinosinusitis, CRS, CRSwNP, nasal polyp, prevalence, disease burden, total polyp score, asthma, biological treatment, EPOS

ABBREVIATIONS

COPD: Chronic Obstructive Pulmonary Disease

CRS: Chronic Rhinosinusitis

CRSsNP: Chronic Rhinosinusitis without Nasal Polyps

CRSwNP: Chronic Rhinosinusitis with Nasal Polyps

ENT: Ear, Nose, Throat

EMA: European Medicines Agency

EPOS: European Position Paper on Rhinosinusitis and Nasal Polyps

FDA: US Food and Drug Administration

FESS: Functional Endoscopic Sinus Surgery

FNE: Flexible Nasal Endoscopy IL: Interleukin

NP: Nasal Polyps

STD: Standard Deviation

TH: T-Helper Cell

TPS: Total Polyp Score

Introduction

Nasal polyposis (NP) is considered a major health problem and until recently, there were only limited treatment options for this disease. The majority of patients are treated with nasal or systemic steroids, nasal douche, long-term antibiotics and/or nasal surgery. Nevertheless, during the last decade, a number of targeted antibody therapies have been developed which, due to their mechanism of action, have the potential to substantially improve disease burden and quality of life in patients with nasal polyposis. However, because of high financial cost these new treatments are likely to be reserved for severely affected patients, who are refractory to standard therapies (1).

Currently there is a gap in the literature regarding the prevalence of patients with nasal polyps differentiated by polyp size and symptom burden. Thus, the number of patients eligible for biological treatment according to current recommendations is unknown. Here we address this question by evaluating various aspects of polyp disease in a large group of patients who underwent nasal endoscopy as part of a routine ear, nose, throat (ENT) examination.

Nasal polyps are non-malignant, inflammatory outgrowths of the nasal respiratory epithelium. Current EPOS guidelines describe nasal polyps as a subgroup of chronic rhinosinusitis (CRSwNP). Additionally for clinical diagnosis at least 2 of the 4 disease defining symptoms (nasal blockage, rhinorrhoea, facial pain and reduced smell) must be present for 3 months or more with at least one of those symptoms being nasal obstruction or rhinorrhoea. Nasal congestion has been shown to be both the most common and the most burdensome problem (1, 2).

Although a number of population studies have been performed with regards to nasal polyp prevalence, they provide limited information on polyp disease burden in Europe and other Western societies. Firstly in terms of prevalence, most of the estimations by large studies relied on patient reporting, record keeping or validated questionnaires to determine the presence of NP (3-7). However, current guidelines recommend corroboration of diagnosis with nasal endoscopy or computer tomography as diagnosis solely based on symptoms leads to over diagnosis (1, 8). Secondly, the largest prevalence studies using nasal endoscopy in line with these guidelines were done in South Korea (9-11). However, the prevalence findings from these studies cannot be extrapolated to European/Western populations, because Asian and Caucasian communities have been shown to have different inflammatory profiles depending on the predominance of the T helper subset. Nasal polyps in both population cohorts are characterised by T effector cell activation as well as impaired regulator T-cell function. However in Caucasian individuals, 80% of polyps are characterized by a Th2 biased cytokine profile (e.g. high expression of IL-5) with a high density of eosinophil infiltrates and are thus classed as Th2 predominant (12) whereas this inflammatory pattern is seen in only 50% of patients in Asian populations with the rest displaying a Th1/Th17 cell bias with neutrophilic inflammation and are thus classed as Th1 predominant (13-15). This differentiation is especially important with a view on biologicals, as the antibodies recently approved by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) target Th2-pathways and IgE. To the best of our knowledge, so far there is only one population-based European study which used the recommended methodology (i.e., nasal endoscopy) in 1387 Swedish patients, of which 38 (2.7%) were found to be affected by nasal polyps (8). However, in this study, neither polyp grade nor symptoms were recorded, likely because of the relatively small absolute

number of patients with polyps. Thus, only the prevalence but not the disease burden was assessed. Thirdly, there are several well performed studies assessing disease burden of NP in detail, but these have been performed in tertiary referral centres, meaning patients with severe disease are likely to be overrepresented (16, 17).

Here we assessed polyp prevalence in a central European community-based population and more than 10,000 patients were included. Diagnosis of nasal polyps was based on examination of the nasal cavities by nasal endoscopy. As a significant number of patients with nasal polyps was identified, we were also able to assess different factors such as age, sex, polyp size, presence of symptoms of chronic rhinosinusitis, impairment of quality of life and disease-relevant comorbidities. In addition, based on these findings, we estimated the proportion of polyp patients that would be eligible for biological therapy based on the recent European guidelines (1).

Methods

Study conduct

The entirety of the study was conducted at a Viennese outpatient ENT facility. The facility is available to all individuals insured through standard national Austrian health insurance programs, who need and/or are wishing to see an ENT specialist. The majority of patients attended the facility without a referral. Retrospective analysis of this patient population was approved by the Ethical Committee at the Medical University of Vienna (EK No. 2218/2018).

Examination procedure

A complete ENT examination including inspection of the middle meatus of the nose by nasal endoscopy with a 2.7mm 30° rigid 14cm (Karl Storz, Tuttlingen, Germany) or using a 4mm flexible nasopharyngoscope (Pentax Europe, Hamburg, Germany) was performed in all patients during at least one visit. Due to the use of thin endoscopes, only in rare cases was the use of a decongestant and/or local anaesthetic necessary in order to examine the nose completely. Examination of the nasal cavity including the middle meatus and documentation of findings was performed in a standardized manner. The presence and size of polyps was graded routinely according to the Gevaert endoscopic grading system, which grades polyps in each nasal cavity from 0-4 (18) 0 = no visible nasal polyps, 1=Small nasal polyps in the middle meatus not reaching below the inferior border of the middle turbinate ; 2=Nasal polyps reaching below the lower border of the middle turbinate ; 3=Large nasal polyps reaching the lower border of the inferior turbinate or polyps medial to the middle turbinate ; 4= Large nasal polyps causing complete obstruction of the inferior nasal cavity Each nasal cavity receives a separate score, thus the total polyp score

(TPS) ranges from 0-8. Polyp grade was written into the patient file separately for each nasal cavity. Patients with unilateral polypoid masses suspicious for either inverted papilloma or nasal cancer were not assessed as having polyps and thus not included in this study. All patients with non-suspicious unilateral polyps were reassessed in 1-3 months to exclude suspicious growth before being included in this study. The same procedure of grading and documentation was used throughout the study duration. All ENT specialists working in the facility as well as assistants helping with note taking were trained in using this standardized documentation system.

Documentation of patients' symptoms and history

Patient history and symptoms were collected taken in three steps: Firstly, all patients were asked about their main reason for attending the facility by the reception staff upon registering. The information the patients gave at this occasion was noted in the electronic file. Secondly, patients were asked about both their ENT symptomatic history and their general medical history by the attending ENT specialist. Furthermore, all patients were prompted to talk about any nose symptoms or presence of nasal allergy immediately before examination of the nose, using the questions: "Do you have any problems with your nose? Do you suffer from allergies?" The resulting data were recorded directly into the electronic file either by the examining ENT specialist or by a trained medical assistant. Patients with nasal polyps were routinely asked whether they were currently on treatment for nasal polyps, had received treatment in the past or undergone nasal surgery in the past. The presence of asthma, allergy and aspirin hypersensitivity were also further clarified. In addition, beginning from March 2018, confirmed polyp patients were routinely asked to fill out a questionnaire specifically asking for the presence and longevity of CRS symptoms. The questionnaire also included the validated Sino-

Nasal Outcome Test-20 German Adapted Version (SNOT-20 GAV) as well as a visual analogue scale (VAS) to assess symptom burden in these patients. The (SNOT-20 GAV) was validated for the German speaking community in 2007. It does not have the same limitations as the original English SNOT-20 as the German translation of this questionnaire included terms covering nasal obstruction “Nasenatmungsbehinderung” and impaired smell “Riechminderung” (19), however it does not have equivalents for item 1 (need to blow nose) and item 13 (Lack of a good night’s sleep) contained in the SNOT-22. Unfortunately at the time of carrying out this study a German translation of the SNOT-22 had not yet been validated. The patients were also asked to clarify their allergic status, whether they had had any previous surgeries for nasal polyps, whether they suffered from aspirin sensitivity, whether they had any diagnosed lung pathology such as Asthma or chronic obstructive pulmonary disease (COPD) and whether they were on any regular medication. For a translated version of the questionnaire please see Fig E1 in this article’s Online Repository at www.jaci-inpractice.org.

Study Populations

For the estimation of polyp prevalence, 10,259 patients consecutively attending a Viennese outpatient ENT facility during the years 2017 to 2019 were included. There were no specific exclusion criteria and all ages and sexes were included. Patients were only excluded if nasal endoscopy was not or could not be performed for any specific reason. A further 114 patients visiting the facility from March 2018 onwards with confirmed nasal polyposis seen during nasal endoscopy were given questionnaires to estimate polyp burden. Patients were asked to complete the questionnaires in a separate room immediately after clinical examination and completed questionnaires were scanned and added to the electronic patient files.

During retrospective data collection, it was found that 13 questionnaires were incomplete with respect to CRS symptomology and/or SNOT-20 GAV, thus these were excluded and 101 fully completed questionnaires were used for subsequent analysis.

Data collection:

From the clinic database, all data was extracted by Rebecca Kohler (RK), who was employed in the ENT facility as a medical assistant. She reviewed each individual patient file and recorded all relevant data in an excel database in a de-personalised form. The following data were collected from all patients of both study populations: Age, sex, main reason for visit, allergic status if available, asthma status if available, TPS if applicable, CRS symptoms if applicable, current medication for polyp patients, previous nasal or sinus operations.

Statistical Analysis

Statistical analysis of the collected data was performed using R version 3.5 and Graphpad prism (Graphpad Prism 7, La Jolla, California, USA). The prevalence of polyps was calculated according to the following formula = $\text{Number of polyp cases} / \text{total cohort} \times 100$. Prevalence was also analysed according to age and sex. For adjustment calculations to estimate the prevalence of polyps in the general Austrian population and the population of the city of Vienna, national population consensus data was used from Statistics Austria (www.statistik.at) and weighted sample estimates were calculated. Weights for each sex and age class combination were derived as the ratio of the proportion of the respective class in the general population and the proportion of the class in the sample. Confidence intervals for weighted estimates were calculated by bootstrapping thereby accounting for sampling variation regarding the prevalence and the calculation of weights. As not all

266 189 patients filled out questionnaires, weighted adjustment calculations for this group
267 was not possible. Therefore adjustment calculations were extrapolated from the
268 weighted calculations made from the main study cohort. For correlations, Pearson's r
269 correlation coefficient was employed. For descriptions of the studied population in
270 terms of demographics, descriptive statistics are shown. Qualitative data are
271 displayed as percentages and quantitative data in terms of mean with standard
272 deviations. For comparison of two data sets, Mann-Whitney test was used, Kruskal-
273 Wallis test was used for comparisons between more than 2 data sets. A p-value
274 below ≤ 0.05 was considered significant.

Results

Characterization of the patient population used for calculation of frequency of nasal polyps

Data from a total of 10,259 subjects who had undergone assessment of their nose during a visit at an ENT outpatient facility in Vienna, Austria, between August 2017 and January 2019 were retrospectively analysed in this study. 55.1% (n = 5657/10,259) of the sampled population were women and 44.9% (n= 4602/10,259) were men. The average age of the cohort was 37.2 years (+/- 19.8 STD; men: 36.8 years +/- 20.0 STD, women: 37.4 years +/- 19.5 STD).

Prevalence of Nasal Polyposis is different between sexes and age groups

The presence of nasal polyps was identified in 1.84% of the sample population (n=189/10,259) and was more common in men (2.56%, n=118/4602) than in women (1.26%, n=71/5656). Polyp prevalence broken down by age groups revealed that the prevalence was highest in age groups of 40-49 and 50-59 years (**Fig. 1A**). Apart from patients under the age of 20, polyps were more common in men than in women in all age groups. Interestingly, polyps were especially frequent in male patients above the age of 70, but rare in women older than 60 years (**Fig. 1B**).

As the age and sex distribution in our study population differed from the distribution in the Viennese and Austrian populations, we performed statistical adjustment calculations in order to estimate general polyp prevalence. This analysis gave an estimated polyp prevalence of 1.91% (95% CI: 1.63%-2.18%) in Vienna and 1.95% (95% CI: 1.66%-2.25%) in Austria.

In the majority of patients, polyps are confined to the middle meatus of the nose

Polyps were graded endoscopically according to the Gevaert Clinical Scoring system which ranges from no polyps (grade 0) to polyps completely obstructing the nasal cavity (grade 4) (18). Each nasal cavity receives a separate score which is combined to the total polyp score (TPS) and thus ranges from 0-8. The frequency and distribution of observed polyp scores in nasal polyp patients is shown in **Fig. 2A**. The average total polyp score was 3.4 (± 1.8 STD) and the majority of polyps were confined to the middle meatus ($TPS \leq 4$) and thus did not extend beyond the superior margin of the inferior turbinate (number of patients with polyps grade (1-2: $n=73$, 3-4: $n=64$, 5-6: $n=37$, 7-8: $n=5$, not scored: $n=10$, total: $n=189$). As polyps have previously been described to be most often symmetrical, it is unsurprising that even polyp scores (i.e., 2, 4, 6 and 8) were more commonly seen than uneven polyp scores. **Fig. 2B** shows that statistical adjustment calculation for age and sex distribution for the Austrian population did not change the polyp score distribution pattern.

Larger polyps are found in male patients and those suffering from asthma

Next we investigated the association of TPS with clinical characteristics (i.e., age, sex, allergy status and presence of asthma). Analysis of the distribution of polyp sizes in different age groups (**Fig. 3A**) revealed that even though polyps were more frequently observed in some age groups, we did not observe any association of the size of polyps with age (Pearson's r correlation coefficient = 0.02, $p=0.77$).

Male patients were found to have significantly higher average TPS than women (average $TPS_{men} = 3.7$ (± 1.8 STD), average $TPS_{women} = 2.8$ (± 1.6 STD), $p=0.0006$), (**Fig. 3B**). A detailed analysis of polyp size distribution in different age groups of male and female patients (Fig. E2 in this article's Online Repository at

www.jaci-inpractice.org) showed that polyp sizes were rather evenly distributed in age groups 20-80+ years. Only those patients who were diagnosed with polyps under the age of 20 (n=5) stood out as having higher polyp scores (average TPS: 5.4 +/- 1.7 STD).

Polyp scores did not differ between allergic and non-allergic polyp patients ($TPS_{allergic} = 3.4$ (+/- 1.7 STD), $TPS_{nonallergic} = 3.4$ (+/- 1.8 STD), $p=0.85$, **Fig. 3C**). In contrast, patients suffering from asthma had significantly larger polyps ($TPS_{asthmatic} = 4.7 \pm 2.1$, $TPS_{nonasthmatic} = 3.2 \pm 1.7$ STD, $p<0.0018$, **Fig. 3D**). Polyp patients with asthma were slightly older (mean age = 46.3 years +/- 14.7 STD) and had a higher proportion of women (60.0%: 12/20) than non-asthmatics (mean age: 43.5 years +/- 16.0 STD, female = 34.9% (n=59/169)). 6.3% (n=12/169) of the polyp patients suffered from AERD.

Only 53% of patients with nasal polyps presented because of nasal symptoms

Upon presentation of patients to the ENT outpatient facility, their main complaint which had prompted patients to make the appointment was documented by the receptionist. Upon retrospective analysis, these complaints were categorised into either nose, ear, throat, headache/facial pain or other complaints (see **Fig. 4**). Within the total sampled population, 19.7% (n= 2023/10,259) had made the appointment because of nose problems, 48.8% (n= 5005/10,259) suffered from ear symptoms, 18.4% (n= 1885/10,259) complained of throat symptoms, 5.1% (n= 525/10,259) had headache and/or facial pain and 8.0% (n= 821/10,259) presented because of other issues (**Fig. 4A**). These numbers were substantially different to the pattern of complaints observed within the polyp cohort, in which more than half of the patients (i.e., 52.9%, n= 100/189) suffered from nasal symptoms, 27.5% (n= 52/189) from ear problems, 4.2% (n= 8/189) had throat symptoms, 4.2% (n= 8/189) complained of

headache/facial pain and 11.1% (n= 21/189) of other issues (**Fig. 4A**). Looking at the frequency of polyps in the patients with these symptom categories, we found that the prevalence of polyps in those complaining of nose symptoms was 4.9%, ear symptoms 1.0%, throat symptoms 0.4%, headache/facial symptoms 1.5% and in other problems 2.5% (**Fig. 4B**).

Symptom burden in polyp patients was assessed using questionnaires

Polyps were found to be “silent” in 19.0% (n=36/189) of patients with polyposis. Meaning these individuals volunteered that they did not have any subjective nasal problems and did not feel they needed any sort of treatment for their nose when asked by the attending physician. The aspect of symptom burden was analysed further in the detailed questionnaires which had been given to patients diagnosed with polyps from March 2018.

Of the 114 available questionnaires, 13 had to be excluded from analysis because they were incomplete with respect to either the type or duration of symptoms. Clinical and epidemiological characteristics of the individual patients for whom questionnaire data were available are listed in **Table 1**. The total polyp population (n=189) and the 101 patients who had completed the questionnaire showed comparable characteristics regarding age (43.8 vs 44.6 years), sex (male: 62.4% vs 69.3%), polyp size (TPS: 3.39 vs 3.41), AERD (6.3% vs 4.1%) and previous nasal surgery (31.7% vs 37.6%).

75% of polyp patients suffer or previously suffered from symptoms of chronic rhinosinusitis

In the questionnaires, patients were specifically asked if and for how long they had suffered from nasal obstruction, rhinorrhoea, facial pain or pressure, or reduction or

loss of sense of smell. According to the EPOS 2020 guidelines, chronic rhinosinusitis is defined by the presence of at least two of these symptoms for more than 3 months, with at least one of the two being nasal obstruction or rhinorrhoea (1). Of the 101 patients, 62 (61.4%) fulfilled this criterion. Of the remaining 39 polyp patients who either had no symptoms (n=17), just one symptom (n=12) or a symptom duration of less than 3 months (n=10), 14 had either previously undergone FESS surgery (n=9/14), or received topical steroid therapy (n=5/14) indicating that they had likely suffered from chronic rhinosinusitis in the past (**Fig. 5A**). The connection between number of CRS-defining symptoms and polyp size is shown in **Fig. 5B**. A statistically significant difference ($p=0.0219$) regarding TPS (data not shown) was found between patients fulfilling the CRS criteria of the current EPOS guidelines (n=62, $TPS=3.77\pm 1.98$ STD) and those who did not (n=39, $TPS= 2.85\pm 1.51$ STD). **Fig. 5C** shows how quality of life, as measured using the SNOT-20 GAV questionnaire, was influenced by polyp size (TPS). Only a weak association was found between these two parameters (Pearson correlation coefficient $r=0.25$, $p=0.0114$). Patients suffering from symptomatic CRS (data not shown) according to EPOS guidelines (1) had a significantly lower quality of life (average SNOT-20 GAV score: 36.8, ± 16.5 STD) than those who did not (average SNOT-20 GAV score: 16.0, ± 11.8 STD; $p<0.0001$).

Analysis of factors of disease severity relevant for indication for treatment with biologicals

According to current EPOS guidelines, treatment with monoclonal antibodies should be considered for those patients with CRSwNP who, after previously having undergone endoscopic sinus surgery, still have bilateral polyps and fulfil at least three of the following criteria: Need for systemic corticosteroids, significantly impaired quality of life, significant loss of smell, diagnosis of comorbid asthma and evidence of type 2

inflammation (1). These evaluation criteria were adapted by us according to the information available from our patients (**Table 2**). While we have data regarding four of these criteria, evidence for presence of type 2 inflammation was not available due to the retrospective nature of the analysis.

Of the 62 patients currently fulfilling the criteria for chronic rhinosinusitis (**Table 1**: #39-100), 29 (#72-100) had previously undergone sinus surgery. Among these patients, 16 (#72-87) were satisfactorily controlled under therapy with topical or systemic corticosteroids. Four patients (#98-101) were already under treatment with biologicals because of their concurrent asthma, while 2 (patients #96-97) have an indication for treatment with biologicals because they fulfil both the mandatory and at least 3/5 of the additional criteria listed in Table 2, even without taking presence of type 2 inflammation into account. A further 8 patients (#88-95) fulfilled both the mandatory and 2 of the additional criteria and therefore may have an indication for treatment with biologicals if they showed evidence for type 2 inflammation. Furthermore, patients #59-71, because of their high level of disease, will likely undergo surgery. Additionally as it is known that in CRSwNP the need for revision surgery is between 10-20% (20, 21) it is to be expected that part of these patients will need treatment with monoclonal antibodies in the future.

Discussion

This study retrospectively investigated the presence of nasal polyps based on the examination of 10,259 patients who underwent nasal endoscopy as part of a routine ENT examination. Nasal polyps were identified in 189 patients (1.84% of the sample population), and extrapolation of our prevalence findings in different age groups resulted in an adjusted prevalence of nasal polyposis in the whole Austrian population of 1.95%. Our findings are in line with the estimates of previous prevalence studies representing the eosinophilic polyp endotype in western populations, which report a prevalence between 2.1 - 4.3% (3-5, 7, 8). However, as symptoms resulting from nasal polyps vary widely, ranging from “silent” polyps to debilitating disease, additional factors need to be taken into consideration in order to understand both disease burden and treatment needs within a population. In our study, we were able to analyse several demographic (age, sex) and clinical factors (total polyp score, concurrent allergy, asthma) in the whole patient population. In addition, in 101 of our patients, questionnaires were available which contained information regarding presence and duration of CRS symptoms (i.e., nasal obstruction, reduction or loss of sense of smell, facial pain and rhinorrhoea) as well as regarding subjective disease severity (VAS) and quality of life (SNOT-20 GAV). Analysis of these questionnaires allowed us to further characterize our patients, with special emphasis on the two ends of the disease spectrum: first, patients with silent polyps without need for therapy and second, those with severe symptoms refractory to standard treatments, thereby making them eligible for treatment with biologicals.

The most common and most bothersome symptom reported by our patients was nasal obstruction, which was present in more than 70% of patients, followed by rhinorrhoea 52.5%, reduced sense of smell 35.6% and facial pain in 17.8%.

Interestingly, a substantial group of patients (38.6%) diagnosed with polyps by nasal endoscopy in our study did not fall into the definition of CRSwNP, which, according to EPOS guidelines, relies on the presence of 2 disease-defining symptoms of rhinosinusitis lasting for more than 3 months (1). Even when we exclude the patients who have a history of symptom altering treatment (i.e., FESS or treatment with biologicals) in the past, 24.8% of patients remain in this category. Our study thus shows that such “silent” or “pre-clinical” polyps in fact represent a significant proportion of patients with visible polyps. Based on our data the prevalence of clinically relevant CRSwNP would be estimated to be only 1.2% of the general Austrian population. Most previous studies investigating polyp prevalence did not specifically investigate the subgroup of patients with silent polyps, either because polyps were diagnosed solely based on endoscopy and data on symptom severity were not available (8) or because data were collected in tertiary referral centres where patient selection is biased towards more severely ill patients.

Data from our prevalence cohort indicate that the size of nasal polyps is small in the majority of patients, with 65% having a total polyp score of 4 or less. Compared to other published data (1, 16, 17, 22-28), this is a low value. However, to our knowledge, ours is the first study to address polyp size in the general population of a Western society and previous descriptions of polyp size are derived from studies conducted in hospital settings (1, 16, 17, 22-28), observing changes upon medication (17) or surgical treatment (16). It could be argued that our cross-sectional retrospective study retains an element of this bias as it was conducted in a specialised ENT facility potentially leading to overestimation of polyp prevalence. However, in our study a large and varied patient population was screened by nasal endoscopy, and Fig. 4 shows that 47.1% of polyp cases were detected in patients who had made their appointment because of a problem unrelated to the nose.

467 Additionally, in Austria due to the healthcare infrastructure any patient can see an
468 ENT doctor without a referral. It is typical for individuals suffering with ENT symptoms
469 to go directly to a community ENT clinic, which is reflected in the fact that a majority
470 of the patients investigated in this study attended the clinic without referrals.

471 Considering almost everyone will suffer with some form of ENT symptom during their
472 lifespan, our data is likely to be representative of the healthcare seeking population in
473 Vienna. However of course patients who do not seek healthcare will be undoubtedly
474 underrepresented. Furthermore, polyp patients with cystic fibrosis are not covered in
475 this study, as this population is managed in specialised centres. In summary, it is
476 likely that the observed features of polyp disease better reflect the true disease
477 burden within the population than studies done in hospital settings. Due to the nature
478 and scope of our cross-sectional study it may be concluded that 1.2% of individuals
479 in central Europe suffer from symptomatic CRSwNP.

480 Another aspect of this study was to see if defined patient characteristics within the
481 polyp cohort were associated with smaller or larger polyps. Although we have found
482 increased prevalence of polyps in older age groups, there was no correlation
483 between higher age and polyp size, which is in agreement with previous studies (1,
484 4). Interestingly, although not statistically significant, patients who developed polyps
485 young (< 20yrs of age) had larger polyps. In line with previous epidemiological data
486 (29, 30) we did not find a significant connection between allergy status and polyp size
487 in our patients, but there was a highly significant difference in the TPS of asthmatic
488 vs non asthmatic polyp patients, which was not influenced by gender distribution or
489 age. It is relatively well established that there are strong associations between
490 asthma and the development of nasal polyps and several studies have shown a
491 higher prevalence of polyps in these populations (1, 3-6, 8). It is therefore interesting

that we have also found a greater polyp size in this group, possibly explained by the increased presence of IL-5 induced eosinophilia and inflammation (1).

Due to the recent success of biologics in treating polyps in phase III clinical trials (17, 18, 31) the FDA and EMA approved both Dupilumab (anti IL-4R α) and Omalizumab (anti-IgE) for the treatment of CRSwNP. In addition, further antibodies targeting pathways known to be involved in chronic rhinosinusitis are being investigated in clinical trials. Currently, there is limited information on how many polyp patients will benefit from or be eligible for their use. In the USA, Naclerio et al recently estimated that as many as 2,000-33,000 patients per year would benefit from biological use in the US alone (32, 33). However, this estimate is based on numbers needing revision sinus surgery and extrapolated data from the proportion of asthmatics that have required biological therapy, and does not consider the recent guidelines published in the recent EPOS 2020 paper (1).

Having this question in view, we adapted the criteria for the initiation of biological therapy (Table 2) to estimate the number of patients in our questionnaire cohort who would be eligible for this treatment. We found that 5.9% (6/101) of our patients would clearly fall into this category. Due to the fact that total IgE and eosinophil levels were not available to us in this retrospective setting, after testing for these parameters a further 8 patients could potentially also be eligible for biological treatment according to EPOS criteria (Table 1, Table 2). Thus, the range of patients eligible for biological treatment is between 6 and 13% of our cohort. It should however also be borne in mind that a recent study looking at the cost/benefit of biologics over standard endoscopic sinus surgery (ESS) found that ESS resulted in a higher quality adjusted life year score and was far cheaper, making it the more cost effective treatment even after multiple surgeries (34). It is thus likely that only part of the patients who are

eligible for antibody therapy will be offered or choose this treatment option.

Additionally our estimate includes polyp patients that are likely receive biological therapy primarily because of Asthma. It is not possible in our study to estimate the number of patients that would benefit from biological therapy only because of polyps as this would require all patients to have undergone lung function testing but future studies investigating this are still needed. Another interesting and important field of application for biologicals is the treatment of patients having contraindications to surgery (e.g. abnormalities of the skull base or orbit and/or medical conditions causing unacceptable risk of anaesthetic) and/or contraindications to systemic steroids but fulfil the other criteria they should be considered for biological therapy (1). This will offer a new treatment option to otherwise difficult to treat patients.

Unfortunately our estimation of patients eligible for biologicals cannot provide insight on the number of patients that may receive them due to these contraindications as none of the patients in our cohort had contraindications to these treatments.

Nonetheless we believe that our data give a useful estimation of the potential number of patients who would benefit from biological therapy and addresses an unmet need in the literature.

In summary, our data assessing disease burden in terms of TPS and symptoms would suggest that although polyps are common, affecting approximately 2% of the general population, a significant portion of these patients either do not have overly burdensome disease in terms of polyp size and symptoms, or can be satisfactorily treated with standard medical therapy and/or endoscopic sinus surgery. Additionally, based on our estimations, a group of patients representing a range of 0.11-0.27% of the general population would, according to their clinical data, be eligible for treatment with biologicals.

542

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546

547 **References**

- 548 1. Fokkens WJ, Lund VJ, Hopkins C, Hellings PW, Kern R, Reitsma S, et al.
549 European Position Paper on Rhinosinusitis and Nasal Polyps 2020. *Rhinology*.
550 2020;58(Suppl S29):1-464.
- 551 2. Rosenfeld RM, Piccirillo JF, Chandrasekhar SS, Brook I, Ashok Kumar K,
552 Kramper M, et al. Clinical practice guideline (update): adult sinusitis. *Otolaryngol*
553 *Head Neck Surg*. 2015;152(2 Suppl):S1-S39.
- 554 3. Klossek JM, Neukirch F, Pribil C, Jankowski R, Serrano E, Chanal I, et al.
555 Prevalence of nasal polyposis in France: a cross-sectional, case-control study.
556 *Allergy*. 2005;60(2):233-7.
- 557 4. Settipane GA, Chafee FH. Nasal polyps in asthma and rhinitis. A review of
558 6,037 patients. *J Allergy Clin Immunol*. 1977;59(1):17-21.
- 559 5. Hedman J, Kaprio J, Poussa T, Nieminen MM. Prevalence of asthma, aspirin
560 intolerance, nasal polyposis and chronic obstructive pulmonary disease in a
561 population-based study. *Int J Epidemiol*. 1999;28(4):717-22.
- 562 6. Shi JB, Fu QL, Zhang H, Cheng L, Wang YJ, Zhu DD, et al. Epidemiology of
563 chronic rhinosinusitis: results from a cross-sectional survey in seven Chinese cities.
564 *Allergy*. 2015;70(5):533-9.
- 565 7. Tan BK, Chandra RK, Pollak J, Kato A, Conley DB, Peters AT, et al. Incidence
566 and associated premorbid diagnoses of patients with chronic rhinosinusitis. *J Allergy*
567 *Clin Immunol*. 2013;131(5):1350-60.

- 568 8. Johansson L, Akerlund A, Holmberg K, Melen I, Bende M. Prevalence of nasal
569 polyps in adults: the Skovde population-based study. *Ann Otol Rhinol Laryngol*.
570 2003;112(7):625-9.
- 571 9. Min YG, Jung HW, Kim HS, Park SK, Yoo KY. Prevalence and risk factors for
572 perennial allergic rhinitis in Korea: results of a nationwide survey. *Clin Otolaryngol*
573 *Allied Sci*. 1997;22(2):139-44.
- 574 10. Won HK, Kim YC, Kang MG, Park HK, Lee SE, Kim MH, et al. Age-related
575 prevalence of chronic rhinosinusitis and nasal polyps and their relationships with
576 asthma onset. *Ann Allergy Asthma Immunol*. 2018;120(4):389-94.
- 577 11. Cho YS, Choi SH, Park KH, Park HJ, Kim JW, Moon IJ, et al. Prevalence of
578 otolaryngologic diseases in South Korea: data from the Korea national health and
579 nutrition examination survey 2008. *Clin Exp Otorhinolaryngol*. 2010;3(4):183-93.
- 580 12. Jankowski R, Bouchoua F, Coffinet L, Vignaud JM. Clinical factors influencing
581 the eosinophil infiltration of nasal polyps. *Rhinology*. 2002;40(4):173-8.
- 582 13. Bachert C, Zhang N, Holtappels G, De Lobel L, van Cauwenberge P, Liu S, et
583 al. Presence of IL-5 protein and IgE antibodies to staphylococcal enterotoxins in
584 nasal polyps is associated with comorbid asthma. *J Allergy Clin Immunol*.
585 2010;126(5):962-8, 8 e1-6.
- 586 14. Zhang N, Van Zele T, Perez-Novo C, Van Bruaene N, Holtappels G, DeRuyc
587 N, et al. Different types of T-effector cells orchestrate mucosal inflammation in
588 chronic sinus disease. *J Allergy Clin Immunol*. 2008;122(5):961-8.
- 589 15. Zhang Y, Gevaert E, Lou H, Wang X, Zhang L, Bachert C, et al. Chronic
590 rhinosinusitis in Asia. *J Allergy Clin Immunol*. 2017;140(5):1230-9.
- 591 16. Calus L, Van Bruaene N, Bosteels C, Dejonckheere S, Van Zele T, Holtappels
592 G, et al. Twelve-year follow-up study after endoscopic sinus surgery in patients with
593 chronic rhinosinusitis with nasal polyposis. *Clin Transl Allergy*. 2019;9:30.
- 594 17. Bachert C, Mannent L, Naclerio RM, Mullol J, Ferguson BJ, Gevaert P, et al.
595 Effect of Subcutaneous Dupilumab on Nasal Polyp Burden in Patients With Chronic
596 Sinusitis and Nasal Polyposis: A Randomized Clinical Trial. *JAMA*. 2016;315(5):469-
597 79.

- 598 18. Gevaert P, Omachi TA, Corren J, Mullol J, Han J, Lee SE, et al. Efficacy and
599 safety of omalizumab in nasal polyposis: 2 randomized phase 3 trials. *J Allergy Clin*
600 *Immunol.* 2020;146(3):595-605.
- 601 19. Baumann I, Blumenstock G, DeMaddalena H, Piccirillo JF, Plinkert PK.
602 [Quality of life in patients with chronic rhinosinusitis: validation of the Sino-Nasal
603 Outcome Test-20 German Adapted Version]. *HNO.* 2007;55(1):42-7.
- 604 20. Hopkins C, Slack R, Lund V, Brown P, Copley L, Browne J. Long-term
605 outcomes from the English national comparative audit of surgery for nasal polyposis
606 and chronic rhinosinusitis. *Laryngoscope.* 2009;119(12):2459-65.
- 607 21. Stein NR, Jafari A, DeConde AS. Revision rates and time to revision following
608 endoscopic sinus surgery: A large database analysis. *Laryngoscope.*
609 2018;128(1):31-6.
- 610 22. Djupesland PG, Vlckova I, Hewson G. Impact of baseline nasal polyp size and
611 previous surgery on efficacy of fluticasone delivered with a novel device: a subgroup
612 analysis. *Am J Rhinol Allergy.* 2010;24(4):291-5.
- 613 23. Yamada T, Fujieda S, Mori S, Yamamoto H, Saito H. Macrolide treatment
614 decreased the size of nasal polyps and IL-8 levels in nasal lavage. *Am J Rhinol.*
615 2000;14(3):143-8.
- 616 24. Gevaert P, Lang-Loidolt D, Lackner A, Stammberger H, Staudinger H, Van
617 Zele T, et al. Nasal IL-5 levels determine the response to anti-IL-5 treatment in
618 patients with nasal polyps. *J Allergy Clin Immunol.* 2006;118(5):1133-41.
- 619 25. Johansson L, Oberg D, Melen I, Bende M. Do topical nasal decongestants
620 affect polyps? *Acta Otolaryngol.* 2006;126(3):288-90.
- 621 26. Hox V, Bobic S, Callebaut I, Jorissen M, Hellings PW. Nasal obstruction and
622 smell impairment in nasal polyp disease: correlation between objective and
623 subjective parameters. *Rhinology.* 2010;48(4):426-32.
- 624 27. Dietz de Loos DA, Hopkins C, Fokkens WJ. Symptoms in chronic
625 rhinosinusitis with and without nasal polyps. *Laryngoscope.* 2013;123(1):57-63.

28. Ryan WR, Ramachandra T, Hwang PH. Correlations between symptoms, nasal endoscopy, and in-office computed tomography in post-surgical chronic rhinosinusitis patients. *Laryngoscope*. 2011;121(3):674-8.
29. Caplin I, Haynes JT, Spahn J. Are nasal polyps an allergic phenomenon? *Ann Allergy*. 1971;29(12):631-4.
30. Perkins JA, Blakeslee DB, Andrade P. Nasal polyps: a manifestation of allergy? *Otolaryngol Head Neck Surg*. 1989;101(6):641-5.
31. Bachert C, Han JK, Desrosiers M, Hellings PW, Amin N, Lee SE, et al. Efficacy and safety of dupilumab in patients with severe chronic rhinosinusitis with nasal polyps (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52): results from two multicentre, randomised, double-blind, placebo-controlled, parallel-group phase 3 trials. *Lancet*. 2019;394(10209):1638-50.
32. Naclerio R, Baroody F, Bachert C, Bleier B, Borish L, Brittain E, et al. Clinical Research Needs for the Management of Chronic Rhinosinusitis with Nasal Polyps in the New Era of Biologics: A National Institute of Allergy and Infectious Diseases Workshop. *J Allergy Clin Immunol Pract*. 2020;8(5):1532-49 e1.
33. Inselman JW, Jeffery MM, Maddux JT, Shah ND, Rank MA. Trends and Disparities in Asthma Biologic Use in the United States. *J Allergy Clin Immunol Pract*. 2020;8(2):549-54 e1.
34. Scangas GA, Wu AW, Ting JY, Metson R, Walgama E, Shrimme MG, et al. Cost Utility Analysis of Dupilumab Versus Endoscopic Sinus Surgery for Chronic Rhinosinusitis With Nasal Polyps. *Laryngoscope*. 2020.

Figure Legends

Fig. 1: Prevalence of nasal polyps by age and sex. (A) Percentage of patients with nasal polyps (y-axis) in different age groups (x-axis) in the studied population. The dashed line indicates the prevalence of nasal polyps within all age groups of the studied population (1.84%). **(B)** Prevalence of nasal polyps (y-axis) across sexes (male=white bars, left panel; female=grey bars, right panel) in different age groups (x-axis). The dotted line represents prevalence of nasal polyps in males (2.56%) and the dashed line depicts prevalence of nasal polyps in females (1.26%).

Fig. 2: Distribution of total polyp scores (TPS) in patients with nasal polyposis. (A) Number of patients (y-axis) in each TPS category (x-axis; n.k. = not known) in the studied population (n=189). **(B)** Estimated prevalence of nasal polyps in the Austrian population (y-axis) by TPS (x-axis) according to statistical adjustment by bootstrapping (see statistical methods, n.k = not known).

Fig. 3: Associations between total polyp score (TPS) and different patient characteristics. (A) Scatter plot of TPS (y-axis) against age (x-axis) in patients with nasal polyps (n=189; Pearson coefficient: $r = 0.02$, $p = 0.77$, n.s.). **(B-D)** Box plot representations of **(B)** TPS vs patient sex, **(C)** TPS vs allergic and non-allergic patients and **(D)** TPS vs asthmatic and non-asthmatic patients. Statistically significant differences are marked above box plot representations: *: $p \leq 0.05$, **: $p \leq 0.01$, ***: $p \leq 0.005$, n.s.: non-significant.

Fig. 4: Primary complaint prompting ENT consultation in the total studied population and in patients with nasal polyps. (A) Main complaint within the total sampled population (n= 10,259, left pie chart) and in patients with nasal polyps (n= 189, right pie chart). **(B)** Polyp patient prevalence expressed as percentage (y-axis) within patients presenting with certain primary ENT complaints in the sampled population.

Fig. 5: Symptom burden in patients with nasal polyps. The presence of acute and chronic symptoms was analysed in polyp patients who had completed a questionnaire (n=101). **(A)** Number of patients (y-axis) reporting to suffer from 0 (black bar) to 4 different typical rhinosinusitis symptoms (i.e., nasal obstruction, rhinorrhoea, facial pain or pressure, reduction or loss of smell) present for less (grey bars) or more (white bars) than three months (x-axis). Numbers above columns indicate the number of patients in the respective group who had previously undergone functional endoscopic sinus surgery. **(B)** Box plot representations of average Total Polyp Score (TPS) (y-axis) against presence of 0 (black bar) to 4 different typical rhinosinusitis symptoms (i.e., nasal obstruction, rhinorrhoea, facial pain or pressure, reduction or loss of smell) present for less (grey bars) or more (white bars) than three months (x-axis). **(C)** Polyp size (total polyp score, x-axis) versus quality of life (Sino Nasal Outcome Test 20 German adapted version (SNOT) score, y-axis). White squares represent patients who suffered from at least 2 chronic symptoms (≥ 3 months duration, n=62), grey squares are patients with either acute symptoms (< 3 months duration), only 1 chronic symptom or no symptoms (n=39).

Table 1. Demographic and clinical characteristics of patients who completed the questionnaire. Sex: m: male, f: female, Polyps Since: New Dg: New diagnosis=questionnaire was completed at the day when the diagnosis of polyps was made; TPS: total polyp score; CRS: chronic rhinosinusitis according to EPOS 2020 guidelines, H: history of chronic rhinosinusitis but does presently not fulfil the criteria of CRS, or history of topical medication; use FESS: functional endoscopic sinus surgery, yes: date of previous FESS unknown; SNOT 20: Sino Nasal Outcome Test, German adapted version 20; Anosmia: Single item SNOT score for anosmia; Asthma: “*”: patients are on long-term inhaled corticosteroid therapy, COPD: chronic obstructive pulmonary disease; ASS: aspirin hypersensitivity; “-”: questionnaire was incomplete regarding this item

Table 2. Indications for biological treatment according to EPOS 2020 criteria and as used in the current study. CRS: chronic rhinosinusitis; ESS: endoscopic sinus surgery; SNOT: Sino Nasal Outcome Test; GAV: German adapted version; yr: year; hpf: high-power field

#	Sex	Age	Polyps Since	Polyp Score	CRS	FESS	Topical Therapy	Systemic Steroids	SNOT	Anosmia	Asthma	Allergy	ASS	Biological?
1	Female	58	<1 year	1/0	No	No	No	No	25	0	Asthma*	Unknown	No	No
2	Female	46	6 years	2/2	No	No	No	No	5	0	No	No	No	No
3	Female	28	New Dg	1/2	No	No	No	No	10	0	No	Unknown	No	No
4	Male	29	New Dg	1/0	No	No	No	No	14	0	No	Yes	No	No
5	Male	32	1 year	1/1	No	No	Yes	No	9	0	No	Yes	No	No
6	Female	51	New Dg	3/0	No	No	No	No	6	0	No	Unknown	No	No
7	Male	56	New Dg	2/0	No	No	No	No	12	0	No	Unknown	No	No
8	Male	81	New Dg	2/0	No	No	No	No	1	0	No	Unknown	No	No
9	Female	41	New Dg	2/0	No	No	No	No	14	0	No	Unknown	No	No
10	Male	50	2 years	2/0	No	No	No	No	8	0	No	Unknown	No	No
11	Male	44	New Dg	1/1	No	No	No	No	21	1	No	No	No	No
12	Male	61	New Dg	2/2	No	No	No	No	20	0	No	No	No	No
13	Male	58	New Dg	1/2	No	No	No	No	39	0	Asthma*	Yes	Unknown	No
14	Male	32	New Dg	1/0	No	No	No	No	6	0	No	Yes	No	No
15	Male	45	New Dg	2/1	No	No	No	No	13	0	No	No	No	No
16	Female	54	8 years	2/1	No	No	No	No	12	0	No	No	No	No
17	Female	57	2 years	2/1	No	No	No	No	5	0	No	No	No	No
18	Male	49	11 years	1/1	No	No	No	No	6	0	No	No	No	No
19	Female	27	<1 year	3/3	No	No	Yes	No	8	0	No	Yes	No	No
20	Male	29	New Dg	2/0	No	No	No	No	24	0	No	No	No	No
21	Male	63	New Dg	2/2	No	No	No	No	22	0	No	Unknown	No	No
22	Female	23	>1 year	2/0	No	No	No	No	5	0	Asthma	Unknown	Unknown	No
23	Male	31	New Dg	1/1	No	No	Yes	No	27	2	No	No	No	No
24	Male	43	New Dg	2/2	No	No	Yes	No	6	0	Asthma	Yes	No	No
25	Male	28	New Dg	3/3	No	No	No	No	7	5	No	No	No	No
26	Male	51	New Dg	2/1	No	No	No	No	0	0	No	Unknown	No	No
27	Male	36	5 years	2/3	No	No	Yes	No	28	2	No	No	No	No
28	Male	65	>1 year	4/3	No	No	No	No	0	0	No	Unknown	No	No

29	Female	41	New Dg	1/1	No	No	No	No	16	0	No	Yes	No	No
30	Female	48	2 years	2/2	H	No	No	No	44	3	Asthma*	Yes	No	No
31	Male	35	>2 years	2/2	H	2018	No	No	43	5	Asthma*	Yes	No	No
32	Male	64	>15 years	3/2	H	2005	H	No	40	1	No	Yes	No	No
33	Male	52	>2 years	1/0	H	2019	H	No	28	1	No	No	No	No
34	Male	43	>1 year	1/0	H	Yes	No	No	15	0	No	Yes	No	No
35	Male	60	2 years	1/0	H	2019	Yes	No	10	1	Asthma*	Yes	No	No
36	Female	51	2 years	1/2	H	Yes	Yes	No	21	1	Asthma*	No	No	No
37	Male	50	<1 year	2/1	H	Yes	Yes	No	24	3	No	Yes	No	No
38	Male	37	New Dg	1/0	H	Yes	No	No	13	0	No	Yes	No	No
39	Male	46	<1 year	1/1	Yes	No	Yes	No	9	0	No	No	No	No
40	Male	52	2 years	1/2	Yes	No	Yes	No	30	2	No	Yes	No	No
41	Male	29	<1 year	1/1	Yes	No	Yes	No	20	0	Asthma	Yes	No	No
42	Female	55	20 years	1/2	Yes	No	Yes	No	32	4	No	No	No	No
43	Male	20	<1 year	1/1	Yes	No	Yes	No	31	4	No	Yes	No	No
44	Male	49	New Dg	0/2	Yes	No	No	No	15	0	No	Yes	No	No
45	Male	53	<1 year	2/0	Yes	No	No	No	9	1	No	No	No	No
46	Male	32	1 year	4/4	Yes	No	Yes	No	25	4	No	No	No	No
47	Male	43	New Dg	4/4	Yes	No	No	No	18	3	No	Unknown	No	No
48	Male	40	New Dg	3/4	Yes	No	No	No	30	4	No	No	No	No
49	Male	59	2 years	1/2	Yes	No	Yes	No	29	2	COPD*	Unknown	No	No
50	Male	50	9 years	3/3	Yes	No	H	No	26	5	No	Yes	No	No
51	Male	36	New Dg	2/2	Yes	No	No	No	51	0	Asthma	Yes	No	No
52	Male	26	New Dg	1/0	Yes	No	No	No	15	2	No	No	No	No
53	Male	38	New Dg	3/0	Yes	No	No	No	48	2	No	Unknown	Unknown	No
54	Female	59	New Dg	2/4	Yes	No	No	No	26	5	No	No	No	No
55	Male	46	New Dg	2/2	Yes	No	No	No	26	5	No	Unknown	No	No
56	Female	30	New Dg	2/0	Yes	No	No	No	26	2	No	Yes	No	No
57	Male	28	7 years	2/4	Yes	No	H	No	67	0	No	No	No	No

58	Male	32	1 year	2/0	Yes	Unknown	Yes	No	15	3	No	No	No	No
59	Male	35	New Dg	2/1	Yes	No	No	No	38	3	No	No	No	No
60	Male	29	1 year	2/3	Yes	No	Yes	No	51	5	No	Yes	No	No
61	Female	64	<1 year	3/3	Yes	No	No	No	40	3	No	Unknown	No	No
62	Male	32	1 year	2/2	Yes	No	Yes	No	50	5	No	Yes	No	No
63	Male	34	New Dg	3/1	Yes	No	No	No	56	5	No	Unknown	No	No
64	Female	20	5 years	3/0	Yes	No	Yes	No	62	5	Asthma	Yes	Yes	No
65	Male	37	New Dg	3/2	Yes	No	No	No	40	4	No	Yes	No	No
66	Male	21	<1 year	2/0	Yes	No	Yes	No	54	0	Asthma*	Yes	No	No
67	Female	30	>1 years	3/4	Yes	No	Yes	No	64	5	Asthma*	No	No	No
68	Male	34	>1 year	2/2	Yes	No	Yes	No	29	3	Asthma*	Yes	No	No
69	Female	54	New Dg	2/1	Yes	No	Yes	No	41	3	Asthma	Yes	No	No
70	Male	22	New Dg	1/0	Yes	No	No	No	46	5	No	Yes	No	No
71	Male	48	New Dg	3/3	Yes	No	No	No	56	4	No	Yes	No	No
72	Male	66	27 years	3/3	Yes	1993	Yes	Yes	33	2	No	No	No	No
73	Male	56	14 years	1/0	Yes	2006	H	No	41	0	No	Unknown	No	No
74	Male	63	10 years	4/4	Yes	2010	No	No	23	5	No	Unknown	No	No
75	Female	56	>8 years	1/1	Yes	2012	Yes	No	17	Missing	No	No	No	No
76	Male	38	3 years	2/2	Yes	2015	No	No	25	1	No	No	No	No
77	Female	20	10 years	2/1	Yes	2015	H	No	13	3	No	No	No	No
78	Female	35	>2 years	1/2	Yes	2017	H	No	27	1	No	Yes	No	No
79	Female	65	13 years	2/2	Yes	2018	H	No	32	5	No	No	No	No
80	Male	58	>2 years	1/0	Yes	2018	Yes	No	15	2	No	Yes	No	No
81	Male	42	>1 year	2/0	Yes	2019	H	No	56	1	No	yes	No	No
82	Male	32	>1 year	2/0	Yes	Yes	H	No	33	4	No	No	No	No
83	Male	58	>1 year	1/0	Yes	Yes	No	No	12	0	No	Unknown	No	No
84	Male	57	1 year	2/0	Yes	Yes	Yes	No	37	0	No	Yes	No	No
85	Male	86	>1 year	4/1	Yes	Yes	Yes	No	32	0	No	No	No	No
86	Female	25	3 years	1/0	Yes	2017	Yes	No	52	4	No	Unknown	No	No

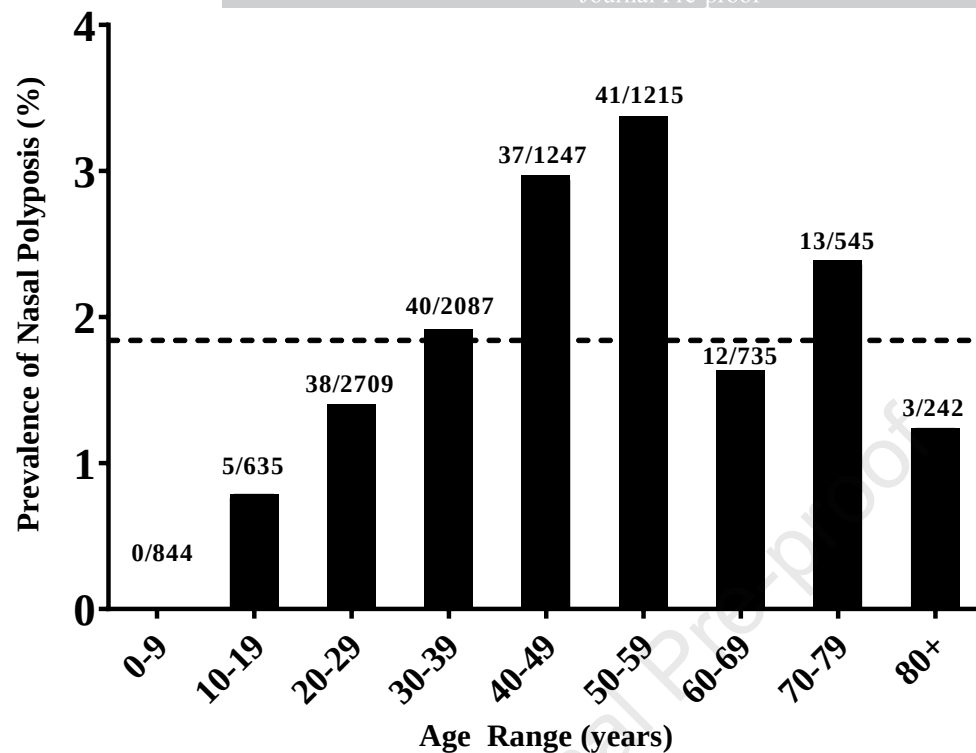
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88	Female	48	12 years	2/2	Yes	2009	Yes	No	56	5	No	Yes	No	No
89	Female	64	14 years	2/2	Yes	2014	Yes	Yes	44	2	COPD*	Yes	No	No
90	Male	50	6 years	4/4	Yes	2014	Yes	No	69	5	Asthma	No	No	No
91	Male	25	3 years	2/3	Yes	2017	Yes	No	51	5	No	Yes	No	No
92	Male	66	2 years	1/2	Yes	2018	Yes	No	48	4	Asthma	Yes	No	No
93	Female	41	2 years	2/3	Yes	2018	Yes	No	59	5	No	Yes	No	No
94	Female	14	4 years	1/1	Yes	2019	Yes	No	55	5	No	No	No	No
95	Male	49	>10 years	4/2	Yes	Yes	Yes	No	32	5	Asthma*	Yes	No	No
96	Male	61	10 years	1/1	Yes	2016	Yes	No	40	4	Asthma*	Yes	No	Yes
97	Female	53	2 years	2/2	Yes	2019	Yes	No	69	5	Asthma*	Yes	Yes	Yes
98	Male	41	> 9 years	4/2	Yes	2011	Yes	No	21	3	Asthma	Yes	No	Yes
99	Female	24	>2 years	2/0	Yes	2018	Yes	No	57	4	Asthma	No	Yes	Yes
100	Female	54	9 years	2/3	Yes	2018	Yes	No	42	5	Asthma	Yes	Yes	Yes
101	Male	52	>8 years	1/1	H	Yes	Yes	No	26	4	Asthma*	Yes	No	Yes

Indications for biological treatment

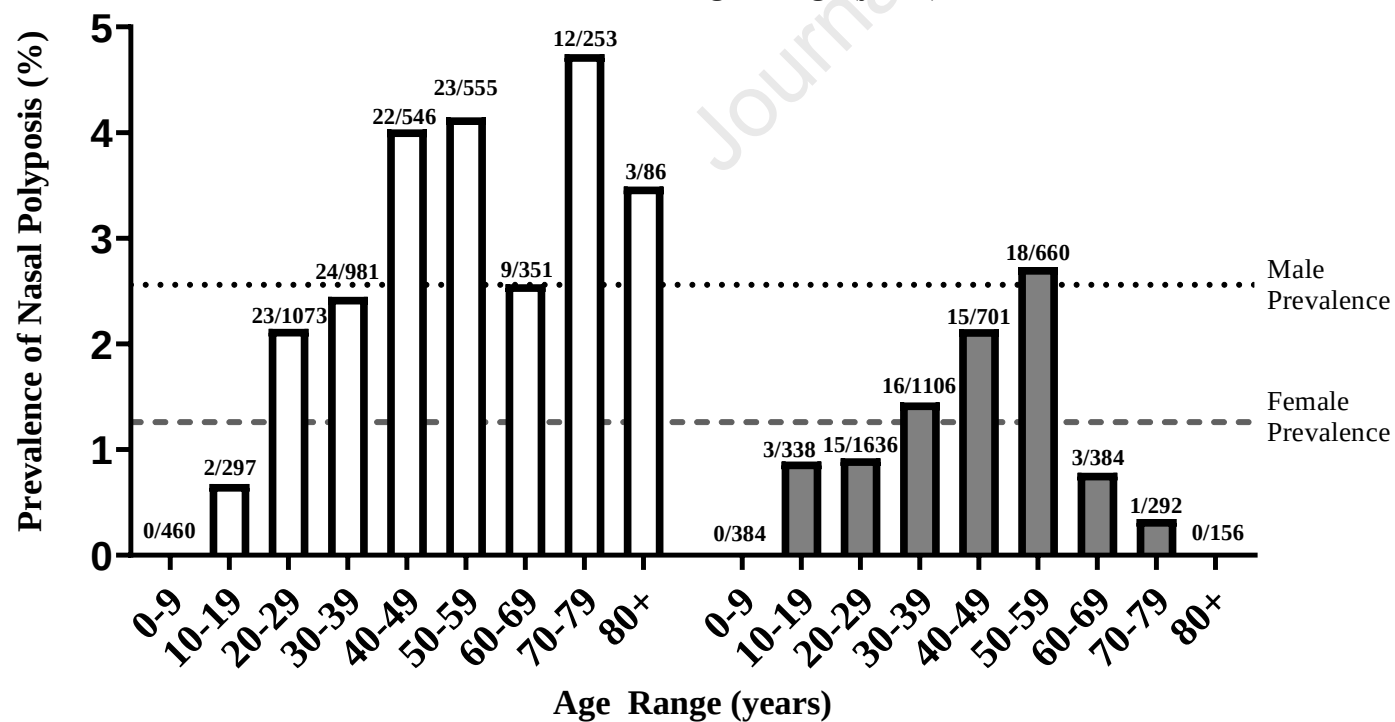
Mandatory Criteria	Active CRS
	Bilateral Polyps
	Previous ESS

		According to EPOS 2020 Guidelines	Adapted for this Study
3/5 Additional criteria required	Significantly impaired quality of life	SNOT-22 ≥ 40	SNOT-GAV-20 ≥ 36
	Significant loss of smell	Anosmic on smell test	SNOT-GAV-20 item 10 "Riechminderung" score ≥ 3
	Need for systemic steroids	≥ 2 courses per yr, OR long term (>3 months) low dose steroids	
	Diagnosis of comorbid asthma	Asthma needing regular inhaled corticosteroids	
	Evidence of type 2 inflammation	Tissue eos ≥ 10 /hpf, OR blood eos ≥ 250 , OR total IgE ≥ 100	Not assessed in this retrospective study

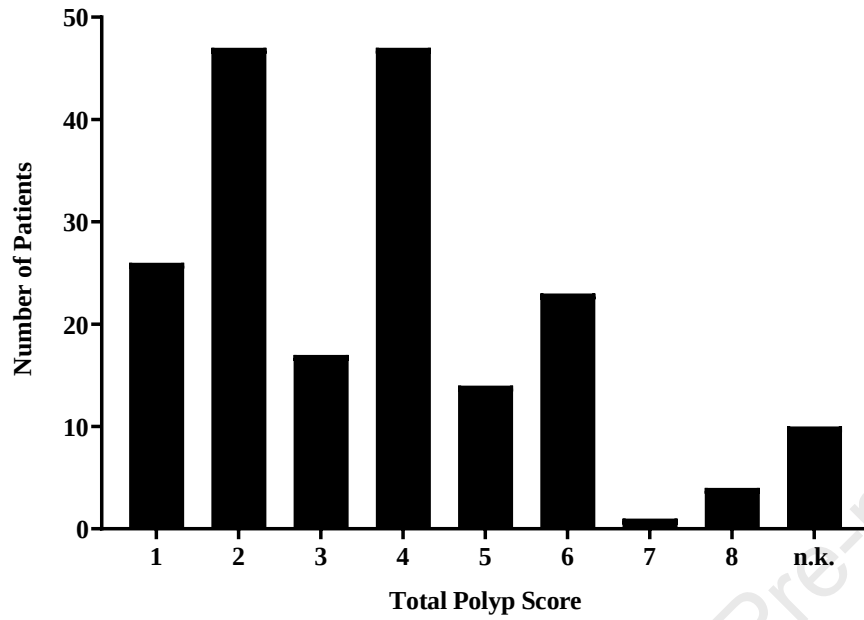
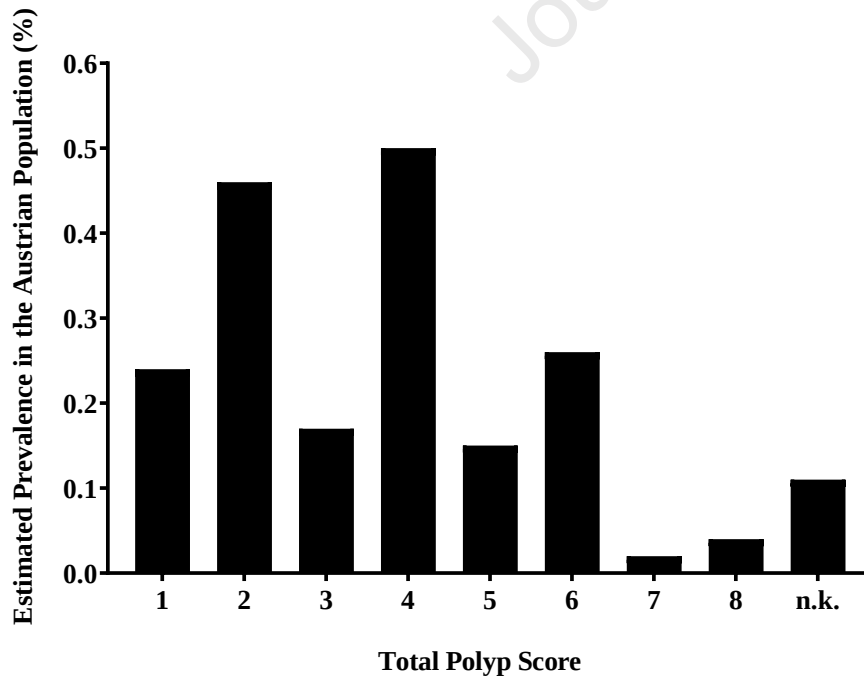
A



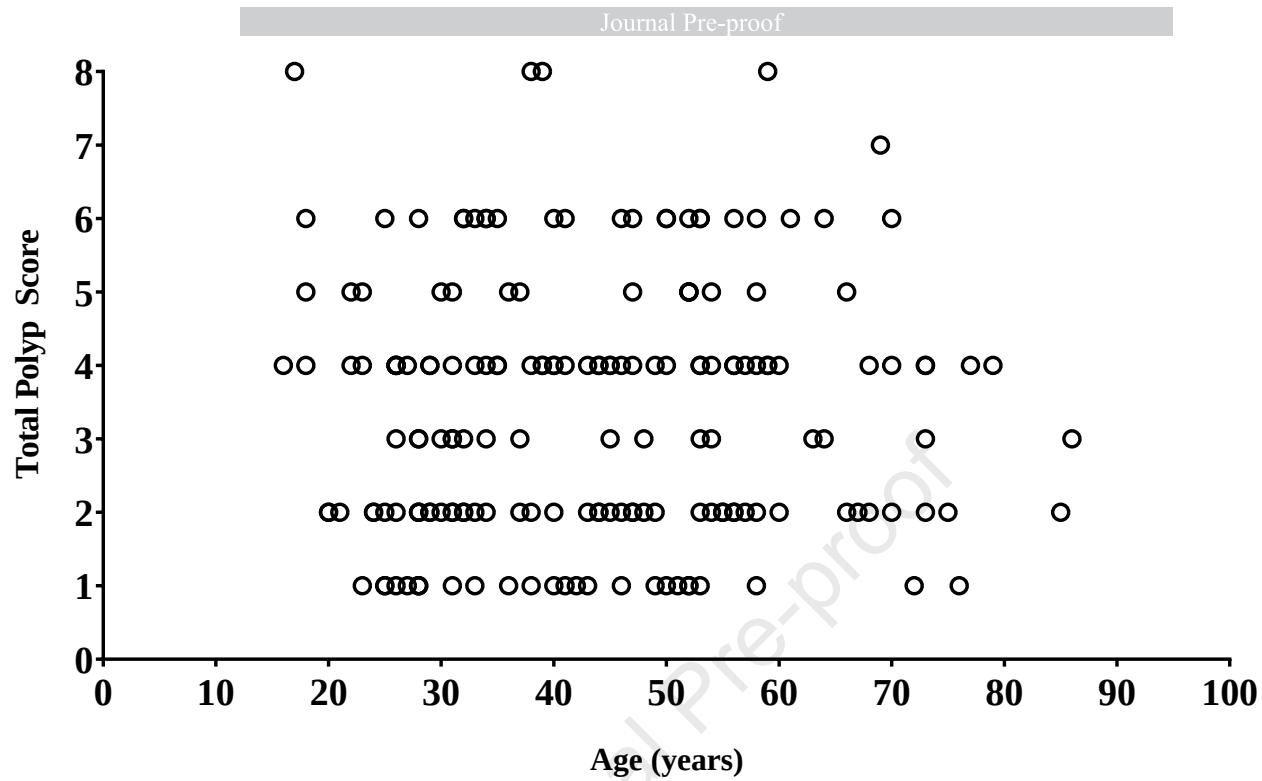
B



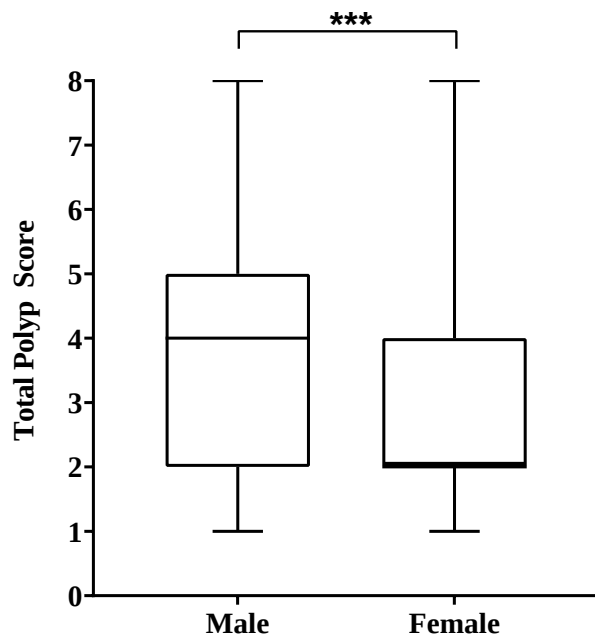
MALE	FEMALE
118	71

A**B**

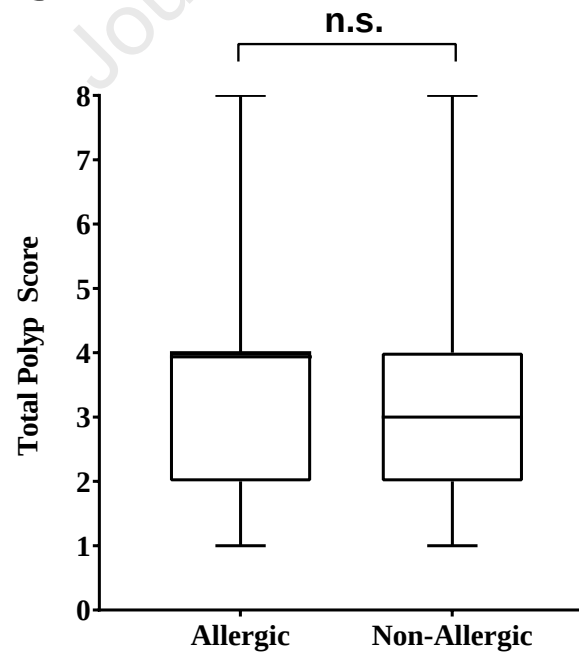
A



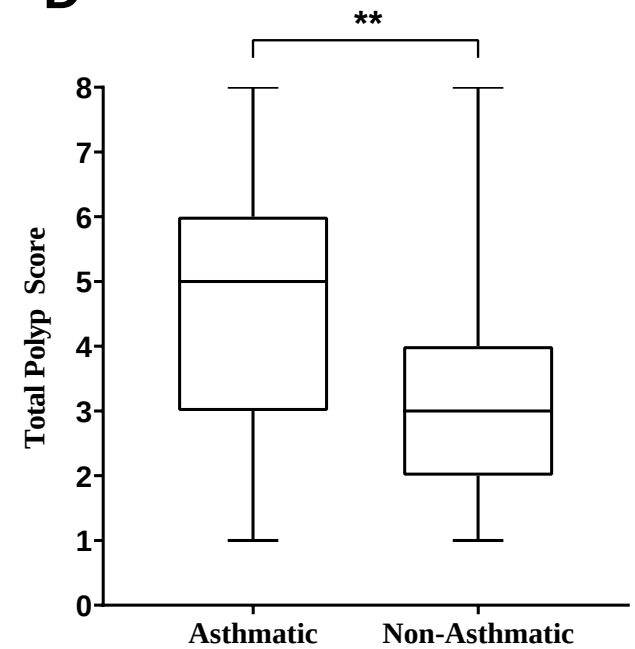
B



C

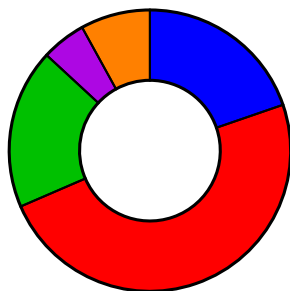


D

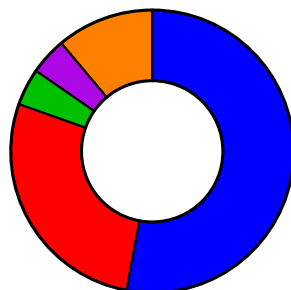


A

Total Sampled Population

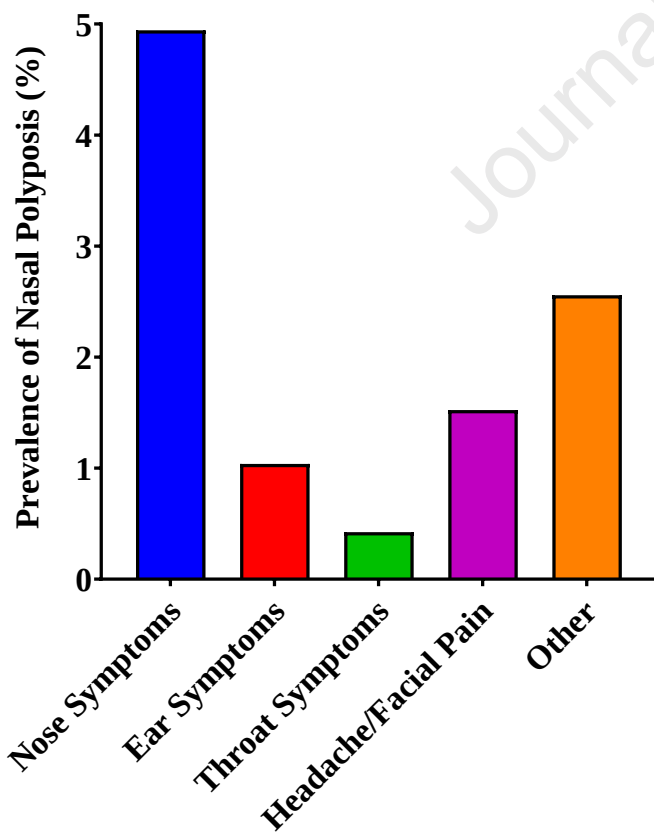


Nasal Polyp Patients



■ Nose Symptoms
■ Ear Symptoms
■ Throat Symptoms
■ Headache/Facial Pain
■ Other

B



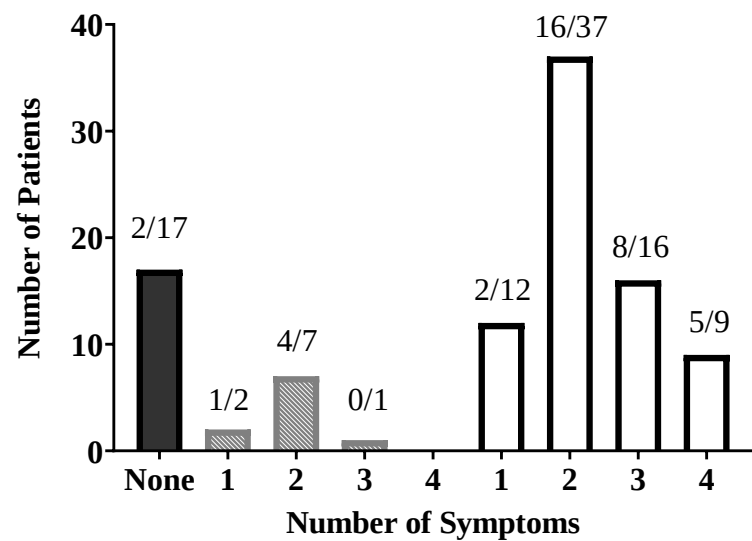
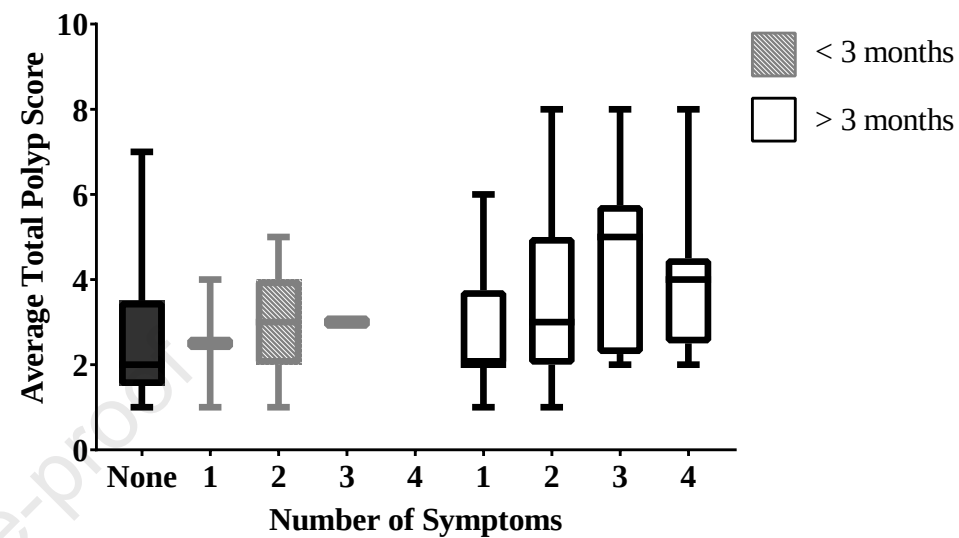
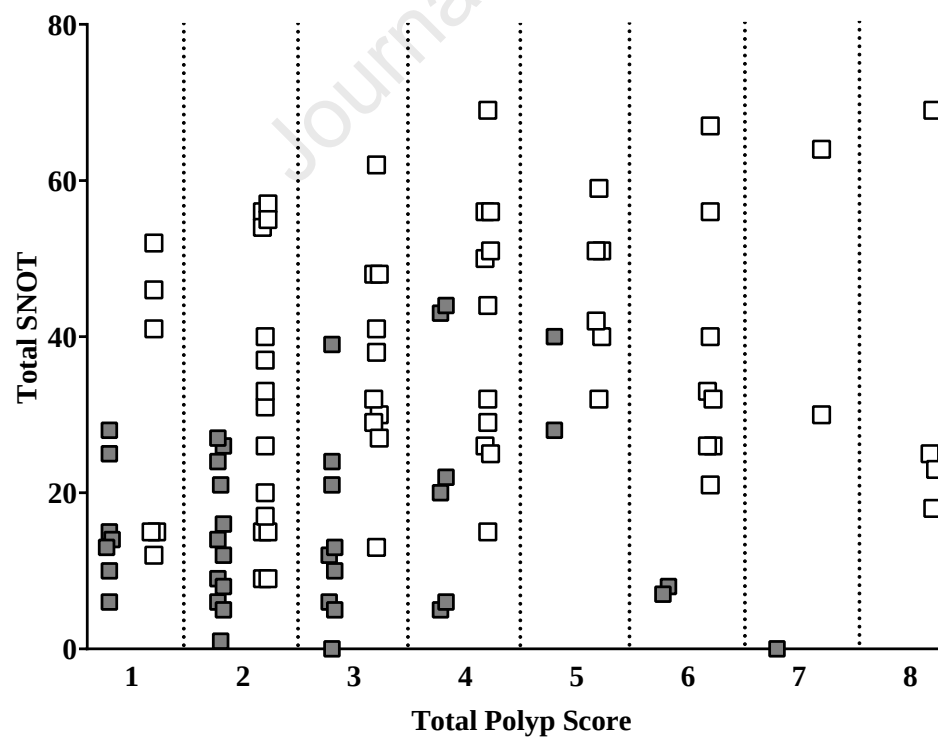
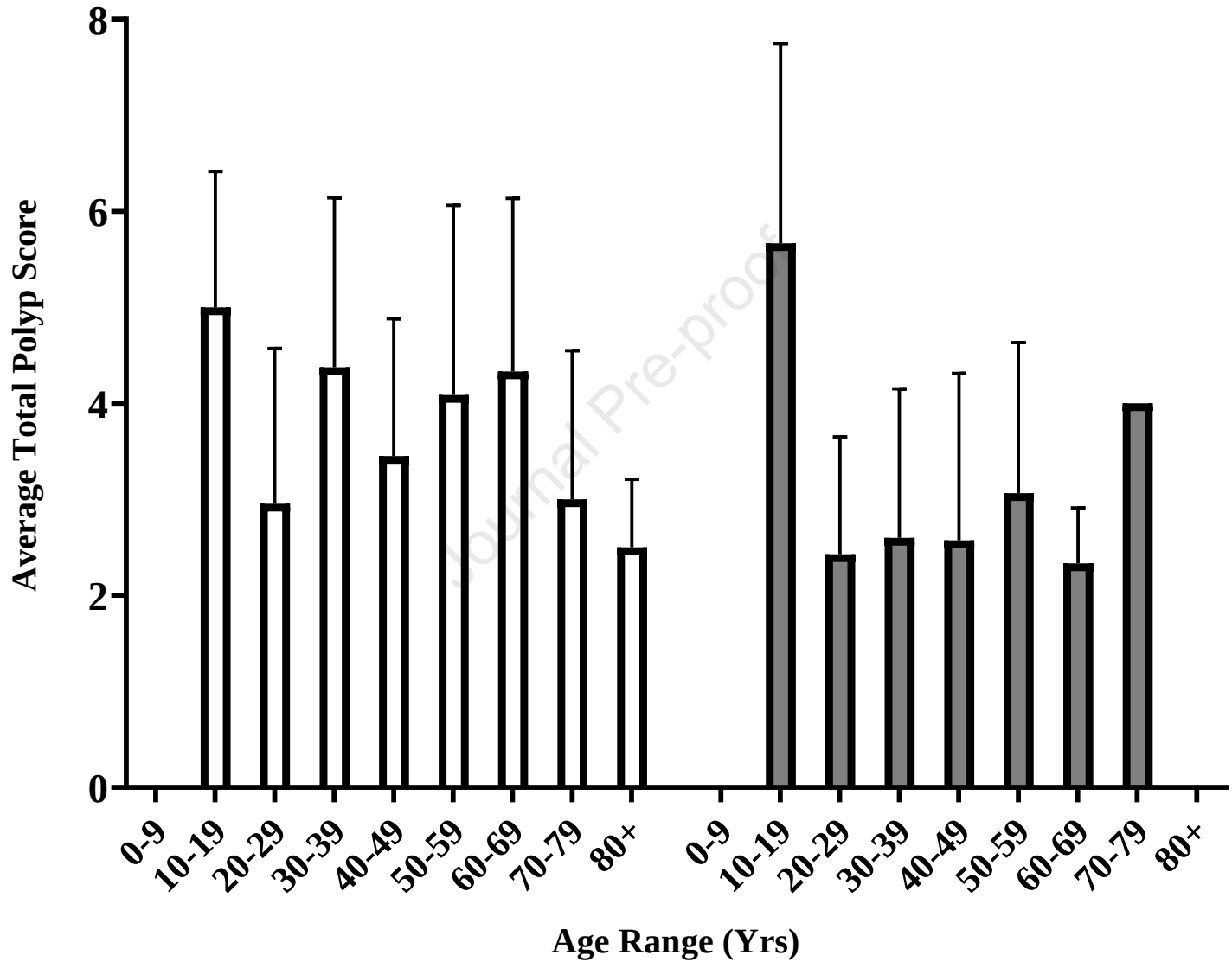
A**B****C**

Figure E1: Questionnaire designed for the acquisition of disease specific and disease affecting parameters

Figure E2: The distribution of mean total polyp scores (y-axis) across age ranges (x-axis) and by gender (male = white bars, female = grey bars). Error bars represent the standard deviation. No statistically significant differences through the use of multiple t tests were detected between any of the groups.

**Male****Female**

Original Questionnaire in German

ANAMNESE NASE

Name Geburtsdatum Datum

Welche Nasenbeschwerden haben Sie und seit wann?

	derzeit nicht	seit bis zu 2 Wochen	seit 2 Wochen bis 3 Monaten	seit mehr als 3 Monaten
behinderte Nasenatmung	☐	☐	☐	☐
Nasenrinnen nach vorne oder hinten	☐	☐	☐	☐
Gesichtsdruckschmerz	☐	☐	☐	☐
Riechstörung	☐	☐	☐	☐

Wurde bei Ihnen schon einmal ein Allergietest durchgeführt? ☐ Ja ☐ Nein

Wann? Was war das Ergebnis?

Wurden Sie an der Nase / den Nasennebenhöhlen operiert? ☐ Ja ☐ Nein

Haben Sie eine Allergie gegen Aspirin? ☐ Ja ☐ Nein

Leiden Sie an einer Lungenerkrankung? ☐ Nein ☐ Asthma ☐ COPD

Nehmen Sie regelmäßig Medikamente ein - falls ja, welche?

English Translation

Nasal Symptom Questionnaire

Name Date of Birth Date

Which nasal complaints do you suffer from and for how long?

	Not currently	Yes but not lasting more than 2 weeks	Lasting more than 2 weeks but less than 3 months	Lasting more than 3 months
Difficulty breathing through the nose	☐	☐	☐	☐
Runny nose and/or post nasal drip	☐	☐	☐	☐
Facial pain	☐	☐	☐	☐
Reduced sense of smell	☐	☐	☐	☐

Have you ever undergone an allergy test? ☐ Yes ☐ No

When? What was the result?

Have you previously undergone a nose and/or sinus operation? ☐ Yes ☐ No

Do you have an allergy towards Aspirin? ☐ Yes ☐ No

Do you suffer from any Lung Diseases? ☐ No ☐ Asthma ☐ COPD

Do you take any regular medication? – if so, which?