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HEALTH-RELATED QUALITY OF LIFE IN RHINOLOGIC PATIENTS

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DOCTORAL DISSERTATION

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The publications are referred to in the text by their Roman numerals.

ABBREVIATIONS

15D	15-dimension generic health-related quality-of-life instrument
ANOVA	Analysis of variance
AR	Allergic rhinitis
ARS	Acute rhinosinusitis
CAD	Coronary artery disease
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CRS	Chronic rhinosinusitis
CRSwNP	Chronic rhinosinusitis with nasal polyps
CRSsNP	Chronic rhinosinusitis without nasal polyps
ePRO	Electronic patient-reported outcome
EQ-5D	EuroQol five dimensions questionnaire
ESS	Endoscopic sinus surgery
EU	European Union
FMI	Finnish Meterological Institute
GBI	Glasgow Benefit Inventory
HMW	High-molecular weight (sensitiser)
HRQoL	Health-related quality of life
HUI	Health Utilities Index
HUS	Helsinki University Hospital
ICC	Intraclass correlation coefficient
ICD-10	International Classification of Diseases, tenth revision
IgE	Immunoglobulin E
ISCO-08	International Standard Classification of Occupations
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
LMW	Low-molecular weight (sensitiser)
MCID	Minimal clinically important difference
MeSH	Medical subject heading
MRI	Magnetic resonance imaging
NAR	Nonallergic rhinitis
OA	Occupational asthma
OR	Occupational rhinitis
OSA	Obstructive sleep apnoea
PCI	Percutaneous coronary intervention
PRO	Patient-reported outcome
PROM	Patient-reported outcome measurement

QoL	Quality of life
RR	Response rate
RSOM-31	Rhinosinusitis Outcomes Measure 31
RUDS	Reactive upper respiratory distress syndrome
SD	Standard deviation
SF-6D	Short-form six-dimension survey
SF-36	36-item short-form survey
SNOT-22	Sino-Nasal Outcome Test 22
TV	Temperature variability
USFDA	United States Food and Drug Administration
WER	Work-exacerbated rhinitis
WHO	World Health Organisation
WRR	Work-related rhinitis

ABSTRACT

Diseases of the nose and sinus (rhinologic diseases) are quite common. It is estimated that almost 11% of Europeans already suffer from chronic rhinosinusitis (CRS) and 23% from allergic rhinitis (AR) alone. Studies on the health-related quality of life (HRQoL) of rhinologic patients have been completed on specific diagnostic groups (CRS and AR patients), but, to our knowledge, none have evaluated unselected rhinologic patients. In our study, we examined the quality of life (QoL) of 337 patients referred to the Helsinki University Hospital's (HUS's) Department of Otorhinolaryngology – Head and Neck Surgery due to rhinologic disease or symptoms in 2014, and then compared the HRQoL for both the population and other patients with chronic diseases to that of rhinologic patients. The generic HRQoL of rhinologic patients was statistically and clinically significantly worse than that for the age- and sex-standardised control population. Moreover, their QoL was also lower than that of many other patient groups (e.g., patients with head and neck cancer or Addison's disease).

In addition, seasonal variation has been reported for many diseases, which may also be related to air temperature and humidity. Seasonal variation affects the morbidity, symptoms, and severity of an illness. Amongst the elderly, the risk of institutionalisation and even mortality increases during the cold winter months. Seasonality has been found in patients with rheumatic diseases, hypertension, and sleep apnoea. Seasonal trends can also be observed in the QoL of the general population. Some research suggests that the season should be taken into account, especially when conducting QoL research. To our knowledge, only one study of the seasonal variation in the HRQoL of rhinologic patients has been previously conducted and applied exclusively to CRS patients. Therefore, we recruited 301 patients from the rhinologic clinic at HUS in 2014 for our study and determined their disease-specific (Sino-Nasal Outcome Test 22, SNOT-22) and general (15-dimension questionnaire, 15D) HRQoL questionnaire during the four seasons. We found no significant seasonal variation in patients' QoL amongst our study population. Notably, however, we identifed very few patients suffered from seasonal allergies (2.3% of study patients). However, given that limitation, we can conclude that these HRQoL questionnaires can be used during clinical follow-up, for example, after surgery, with no significant impact from the seasons.

In addition, exposure to specific occupational sensitisers (low-molecular weight [LMW] and high-molecular weight [HMW] sensitisers) or irritants serves as a risk for the development of chronic rhinitis and rhinosinusitis. However, little is known about the role of occupational exposure on patients' rhinologic

symptoms. Moreover, the HRQoL of rhinologic patients and its relationship to occupational exposures has primarily been studied amongst patients with rhinitis. Our study, then, aimed to assess the extent to which patients referred to specialist care due to rhinologicF diseases exhibited worsening rhinologic symptoms at work and whether these were related to exposure to specific work-related sensitisers or irritants. Exposure was also compared to both disease-specific and generic HRQoL. In addition, we also examined the need for sick leave reported by patients due to their rhinologic disease during the preceding year. For the 177 unselected adult rhinologic patients in employment recruited for our study, we found that exposure to specific occupational exposures did not affect patients' symptoms at work or their HRQoL. However, the majority of rhinologic patients reported disease exacerbation at work. It appears that their increasing symptoms were, therefore, more likely related to unspecific respiratory triggers. In our study, we found that rhinologic diseases cause substantial work absenteeism.

Furthermore, HRQoL has traditionally been evaluated using paper questionnaires. However, in order to implement HRQoL measurements in everyday clinical practice and, thus, increase the amount of HRQoL data available, efforts have recently focused on converting the forms to electronic formats. Our study aimed to determine whether the generic 15D questionnaire can be converted to an electronic format without impacting its reliability and measurement equivalence or diminishing the response rates (RRs). We also assessed patient experiences and preferences between different formats. To do so, we recruited 159 patients from the Department of Otorhinolaryngology at HUS between April and June 2019 for our study and randomised them into four different study groups. In each group, patients completed the paper version of the 15D and one of two electronic versions (a web-based or an application-based format). Based on our findings, the 15D can be converted to an electronic version without compromising its reliability. Patients also preferred electronic formats (74.1%) over paper versions (16.5%). However, the RRs for the electronic surveys remained lower than that for the paper-based questionnaire.

To conclude, we found that the HRQoL of rhinologic patients seems to decrease and does not show marked seasonal variation. Patients reported symptom exacerbation at work, but this was not clearly related to specific occupational exposures. Absenteeism due to rhinologic diseases remains high. As such, rhinologic diseases cause a remarkable burden both to the individual and to society as a whole.

TIIVISTELMÄ

Nenä- ja sivuontelosairaudet (rinologiset sairaudet) ovat hyvin yleisiä. Pelkästään pitkäaikaista sivuontelotulehdusta (CRS) sairastaa arviolta jo lähes 11 % ja allergista nuhaa 23 % eurooppalaisista. Rinologisten potilaiden elämänlaadusta on paljon tutkimustuloksia, mutta tutkimukset ovat koskeneet yksittäisiä diagnoosiryhmiä. Tutkimusaineistomme koostui valikoimattomasta 337 rinologisen potilaan joukosta. Potilaat oli lähetetty vuoden 2014 aikana Helsingin yliopistolliseen keskussairaalan korva-, nenä- ja kurkkutautien klinikalle rinologisen sairauden tai oireen vuoksi. Vertasimme potilaiden elämänlaatua sekä koko väestön että muiden kroonisista sairauksista kärsivien potilaiden elämänlaatuun. Rinologisten potilaiden yleinen elämänlaatu oli merkittävästi huonompi kuin ikä- ja sukupuolivakioidulla verrokkiväestöllä. Heidän elämänlaatunsa oli myös heikompi kuin monella muulla potilasryhmällä (esimerkiksi pään ja kaulan alueen syöpää tai Addisonin tautia sairastavilla potilailla).

Monissa sairauksissa esiintyy selvää vuodenaikavaihtelua, jonka on todettu liittyvän muun muassa ilman lämpötilaan ja kosteuteen. Vuodenaikavaihtelu vaikuttaa sairastuvuuteen, oireisiin ja sairauden vaikeusasteeseen. Vanhuksilla riski laitostumiseen ja jopa kuolleisuus lisääntyvät kylminä talvikuukausina. Vuodenaikavaihtelua on todettu olevan esimerkiksi reumasairauksista, korkeasta verenpaineesta ja uniapneasta kärsivillä potilailla. Myös väestön elämänlaadussa on nähtävillä vuodenaikavaihteluita. Onkin esitetty, että vuodenaika tulisi ottaa huomioon erityisesti elämänlaatua koskevia tutkimuksia tehtäessä. Rinologisten potilaiden elämänlaadun vuodenaikavaihtelusta ei ole tietääksemme tehty kuin yksi ainoastaan CRS-potilaita koskeva tutkimus. Rekrytoimme vuonna 2014 tutkimukseemme 301 Helsingin yliopistollisen keskussairaalan rinologisen poliklinikan potilasta ja selvitimme heidän tautispesifisen ja yleisen elämänlaatunsa neljänä eri vuodenaikana. Tutkimuspotilaiden elämänlaadussa ei ollut merkittävää vuodenaikavaihtelua. On kuitenkin huomioitava, että aineistossa oli hyvin vähän kausiallergiasta kärsiviä potilaita (2,3 % tutkimuspotilaista). Tämä rajoite huomioon ottaen voimme kuitenkin todeta, että tutkittuja elämänlaatukaavakkeita voidaan käyttää esimerkiksi leikkauksen jälkeisessä seurannassa ilman, että vuodenaikaa tarvitsisi merkittävästi ottaa huomioon.

Spesifeille työperäisille sisäilma-altisteille (pienen molekyylipainon [LMW] ja suuren molekyylipainon [HMW] altisteet) altistuminen on riskitekijä kroonisen nuhan ja sivuontelotulehduksen kehittymiselle. Työperäisten altisteiden merkityksestä potilaiden rinologisiin oireisiin on kuitenkin hyvin vähän

tietoa. Rinologisten potilaiden elämänlaatua ja sen yhteyttä työn altisteisiin on tutkittu pitkälti vain nuhapotilailla. Tutkimuksemme tarkoituksena oli arvioida Helsingin yliopistollisen keskussairaalan rinologiselle poliklinikalle lähetettyjen valikoimattomien potilaiden aineistosta, missä määrin rinologisten sairauksien takia erikoissairaanhoitoon lähetetyillä potilailla on työssä pahenevia rinologisia oireita. Arvioimme myös, liittyvätkö nämä työilman epäpuhtauksille altistumiseen ja millaisia mahdollisesti merkitykselliset altisteet ovat. Altistumista verrattiin myös sekä tautispesifiseen että yleiseen elämänlaatuun. Lisäksi tutkimus selvitti potilaiden ilmoittamaa nenän sairauksiin liittyvää sairausloman tarvetta viimeisen vuoden aikana. Havaitsimme 177:n tutkimukseemme rekrytoidun valikoimattoman rinologisen klinikkapotilaan aineistosta, että spesifeille työperäisille altisteille altistuminen ei vaikuttanut potilaiden oireisiin työssä eikä heidän elämänlaatuunsa. Pääosa tutkimuspotilaista kuitenkin koki, että heidän oireilunsa lisääntyi töissä. Todennäköisesti heidän oireilunsa liittyikin näin ollen epäspesifeihin sisäilmaärsykkeisiin. Tutkimuksemme osoitti myös, että rinologiset sairaudet lisäävät selvästi potilaiden sairauspoissaoloja ja potilaat ovat niiden vuoksi sairauslomalla keskimäärin 7,7 päivää vuodessa.

Potilaiden elämänlaatua on kartoitettu perinteisesti paperisilla lomakkeilla. Tutkimustiedon helppokäyttöisyyden ja laajempien tutkimusaineistojen kokoon saamiseksi on kuitenkin jo pitkään pyritty saattamaan kaavakkeet sähköiseen muotoon. Tutkimuksemme tarkoituksena oli selvittää, voidaanko yleistä elämänlaatua mittaava 15D-kysely siirtää sähköiseen muotoon ilman, että sillä on vaikutuksia tutkimuksen tuloksiin. Halusimme myös selvittää potilaiden kokemuksia eri lomakemuotojen välillä. Tutkimusaineistomme koostui 159:stä Helsingin yliopistollisen keskussairaalan rinologisen ja otologisen poliklinikan potilaasta. Havaitsimme, että 15D-kaavake voidaan siirtää sähköiseksi versioksi ilman, että sen luotettavuus kärsii. Potilaat myös pitävät sähköisistä lomakemuodoista enemmän kuin paperisista. Vastausasteet sähköisissä kyselyissä jäivät paperisia kyselyitä matalammiksi.

Nenä- ja sivuontelosairauksista kärsivien potilaiden elämänlaatu on alentunut eikä selvää vuodenaikavaihtelua havaita tässä tutkimuksessa. Rinologisten potilaiden oireilu hankaloituu töissä, mutta tämä ei liity erityisesti spesifeihin työperäisiin altisteisiin. Rinologiset potilaat ovat sairauslomalla keskimääräistä työntekijää enemmän. Rinologiset sairaudet siis rasittavat huomattavasti sekä potilasta että yhteiskuntaa.

1 INTRODUCTION

In recent decades and alongside objective findings, more explicit attention has been devoted to subjective well-being in assessing patients' responses to treatment or illness severity. Quality of life (QoL) and, in particular, health-related quality of life (HRQoL), is of growing interest to both clinicians and researchers. Numerous instruments have been published to evaluate patients' HRQoL (1). More specifically, HRQoL instruments fall into two categories: generic and disease-specific measurements. Generic HRQoL tools focus on a patient's social, physical, and mental well-being, whilst disease-specific surveys examine the typical features of each disease. Generic measurements are useful in comparing, for example, different disease groups, although disease-specific instruments are often more accurate in detecting small, clinically significant differences in patients' QoL (2). Therefore, it is often recommended that these two instruments are used concurrently (3).

HRQoL surveys have primarily relied on paper formats, although growing interest has surrounded electronic administration of measurement instruments. The benefits of electronic formats are manifold. For instance, they are time-efficient, improve data quality, and facilitate clinical work and research (4). When using electronic HRQoL instruments, it must be possible to demonstrate that respondents complete the electronic versions in the same way as their paper formats in order to render the two versions comparable and equivalent. Thus, comprehensive guidelines have been developed for this purpose by the International Society for Pharmacoeconomics and Outcomes Research's (ISPOR's) electronic patient-reported outcome (ePRO) working group (5).

Rhinologic diseases refer to diseases localised to the region of the nose and sinuses. Such diseases are quite common and each of us has likely experienced them, at least in the form of acute rhinitis. However, chronic and acute rhinosinusitis as well as allergic rhinitis also affect up to 5–40% of the population (6-10). The importance of rhinologic diseases to society is considerable. In the US, the total annual cost of chronic rhinosinusitis (CRS) is estimated to approach that for asthma (US$64.5 billion vs US$81.9 billion) (11, 12), with illness carrying both direct and indirect costs. Direct costs consist of, amongst other things, doctor visits and examinations, as well as patients' medicines. Indirect costs, by contrast, consist of sick leave and a reduced ability to work. In 2020, sickness absences per employed person in Finland reached 9.1 days (13). More specifically, CRS is associated with 8–14 work days (14) and allergic rhinitis (AR) results in 0.6–9.9 work-days lost (15, 16), although no previous study data on sick leaves related to other rhinologic patients were found.

In addition to economic considerations, the burden of rhinologic diseases on patients is significant. QoL in rhinologic patients has been studied, but largely only in the most common diagnostic groups, such as CRS and AR (17, 18). The negative impact of these diseases on HRQoL has been found to exceed that of many other chronic diseases, such as Parkinson's disease and obesity (17). One explanation for the poor QoL amongst rhinologic patients lies in comorbidities. Rhinologic patients often have asthma, sleep apnoea, or depression (19-21). Furthermore, rhinologic diseases are also sensitive to patients' sleep, and the role of sleep problems in deteriorating QoL is undeniable (20, 22).

Many diseases vary seasonally. Seasonal variation can impact a patient's symptoms, disease progression, and even mortality (23-37). Furthermore, some rhinologic diseases reportedly have a seasonal variation. For example, epistaxis and acute exacerbations of CRS peak in frequency during winter (38-40). QoL also seems to vary with the seasons, but the objective evidence of this remains limited (41-43).

Occupational exposures can aggravate or even cause illness (44, 45). Respiratory exposures can be divided into two groups according to their molecular weight, and amongst these, high molecular weight (HMW) exposures in particular cause respiratory difficulties. There are numerous studies on the effects of occupational exposures in asthma patients (45-49). In addition, publications on the occupational symptoms of rhinitis patients exist, although considerably fewer (50-53). However, it has been estimated that occupational rhinitis may be up to 2–4 times more common than occupational asthma (54). Occupational CRS has also been studied to some extent (55-58), but little is known about the effects of occupational exposures on symptoms or the QoL of other rhinologic patients.

In this thesis, we examined the general and disease-specific HRQoL of patients with different rhinologic diseases, comparing HRQoL to patients with other diseases and to the general population. The seasonal variation of the HRQoL amongst rhinologic patients was also evaluated. The HRQoL and symptoms of rhinologic patients at work were also examined and the association between relevant occupational irritant exposures and symptoms were analysed. We also examined absenteeism amongst rhinologic patients. Finally, we assessed the feasibility of converting a paper 15-dimension generic health-related QoL form (15D) to an electronic version.

2 REVIEW OF THE LITERATURE

2.1 Patient-Reported Outcomes (PROs)

In recent decades, data from patient-reported outcomes (PROs) have been increasingly collected and used initially in clinical trials as well as in everyday clinical work. PRO is a general term that includes many other self-reporting tools in addition to HRQoL questionnaires and is one of many clinical outcome evaluation methods complementing clinical trials. The United States Food and Drug Administration (USFDA) defines PRO as 'any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else' (59). Technological advancements in health care, including electronic patient records and various computer applications, have been adopted worldwide. Still, until recent years, patient-reported outcome measurements (PROMs) have primarily been administered using paper formats. However, the need for electronic data platforms has rapidly emerged, with estimates suggesting that the ePRO market will triple between 2020 and 2027 (60). The benefits of electronic data collection methods are vast. For example, such methods are time-efficient for both patients and researchers, potentially cost-saving, more reliable, and allow for the routine collection of patients' QoL data in daily clinical practice (4). Furthermore, electronic data can be collected using web-based questionnaires or different kinds of mobile applications.

2.1.1 An electronic PRO measurement (PROM)

There are two ways to create an electronic PROM: creating a completely new electronic survey directly or converting and validating an existing paper-based questionnaire into an electronic format. In the latter option, an ePRO questionnaire should produce data equivalent or even superior to the data obtained from the original paper version (5). According to ISPOR's ePRO working group's good research practice recommendations, when implementing an electronic version, the degree of changes in the paper format determine the extent to which the formats are comparable and whether the introduction of an electronic format requires an equivalence study (5, 61). The three levels of recommendations for assessing measurement equivalence appear in Table 1 (5). In contrast to these recommendations, Muehlhausen et al. stated in a large review article in 2015 that data exist to support the idea that not all moderate

changes require quantitative equivalence testing, although this is still not established (62).

Table 1. ISPOR's recommendations for assessing measurement equivalence (modified from Coons et al. (5))

Degree of change	Example	Recommendation
Minor	Convert the paper format to an electronic version No change in content or meaning	Cognitive debriefing Usability testing
Moderate	Change to the order of item presentation Require the patient to use a scroll bar to view all item text or responses	Equivalence testing Usability testing
Substantial	Change the text of items Remove items or scale options	Full psychometric testing Usability testing

Cognitive debriefing is a process whereby the questionnaire is tested amongst a study population in order to verify unclear questions and other sections that may be difficult to understand (63). Testing the usability of a survey refers to ensuring that the study population is able to respond to that survey format. In the case of an ePRO, testing usability specifically means determining with some certainty that respondents know how to use a particular electronic device (64). Equivalence testing is a more complex procedure, the purpose of which is to evaluate the comparability between PROM scores from the electronic version and from the original paper version. Finally, full psychometric testing indicates that the electronic format is treated as a new PROM (65).

Two different study designs are recommended for equivalence testing. First, a randomised parallel group design involves half of study patients completing a paper version PRO whilst the other half completes an ePRO version. The second design involves a randomised crossover design, whereby all patients complete both the paper PRO and the ePRO formats. The crossover design appears more efficient than the parallel group design and is, therefore, more often selected as the method for equivalence testing (66). Researchers should take into account that the wash-out period (e.g., the time between the completion of the different forms) is the proper length: not too short to minimise memory, but not too long to avoid changes in a patient's health status (5, 67). No consensus exists regarding the specific interval for this test–retest reliability, although in previous PROM equivalence studies this time frame primarily consisted of 0–15 days (62, 68).

According to Coons et al. (2009), the intraclass correlation coefficient (ICC) is the recommended statistics for use for assessing measurement reliability comparing paper and electronic PROMs. But, remarkably, ICC is only applicable for crossover study designs (5). There are different formats of ICCs, such that researchers should always specify the ICC they use in their analysis. The ICC value ranges from 0 to 1 based on the 95% confidence interval (CI) of estimates. It is recommended that the 95% CI of the ICC estimate, and not the ICC estimate

itself, should be used when evaluating the level of reliability. Values below 0.5 indicate a poor reliability, values between 0.5 and 0.75 indicate a moderate reliability, values between 0.75 and 0.9 indicate a good reliability, and values above 0.9 indicate an excellent reliability (69). A value of at least 0.7 for the ICC is typically considered sufficient.

The measurement equivalence between the paper PROM format and the electronic version has been extensively studied, with encouraging results indicating that the formats appear equivalent (62, 66, 70-76). The mode of ePROM administration also appears to have no significant impact on the reliability or validity of the questionnaire (77).

2.1.2 Patient preferences for the mode of administration and response rates (RRs)

When considering converting PROMs to an electronic format, it is important to evaluate not only patient preferences but also response rates (RRs). According to multiple published studies, patients prefer electronic formats, althgough this is strongly influenced by the patient's socioeconomic background, age, sex, and other characteristics — that is, the lower the level of education and income of a patient and the older they are, the more likely they are to prefer a paper version (4, 78-83). Data from RRs comparing different PROM formats are contradictory, although the trend appears to indicate that ePROs carry somewhat lower RRs than paper-based versions (4, 81, 84-86). According to a review article by Rutherford et al., the differences in RRs are due, at least partially, to the heterogeneity of the research settings (74). However, there is strong evidence that optimising the content and presentation of the survey questionnaire and using different reminder messages can positively influence RRs (79, 86-88). Presumably, integrating such reminders into an electronic system is not excessively time-consuming or costly.

2.2 Health-Related Quality of Life (HRQoL)

As stated in a World Health Organisation (WHO) publication as early as 1949, QoL is often defined as 'an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns' (89). In the medical literature, QoL has been reported since at least since the 1960s (90), with the importance of QoL in medical decision-making and its role in medical research increasing substantially in the last two decades. A literature search of the medical subject heading (MeSH) terms 'quality of life' or 'health-related quality of life' in Pubmed returns hundreds of thousands of publications and the number of publications

has increased tenfold over the last two decades. The definition of HRQoL is not as simple, with several different definitions appearing in the literature. However, HRQoL can be distinguished from QoL given that it focuses on the impact of an illness, symptoms, or a particular treatment on an individual's QoL (90). Health is one of the factors regulating a person's QoL and in a survey amongst a random adult sample, respondents chose health as one of the most important aspects of life (91).

2.3 HRQoL Measurement Tools

In order to evaluate HRQoL, specific questionnaires have been developed. The first HRQoL instrument, the QL index, was published in 1981 for cancer patients (92). HRQoL questionnaires include several dimensions. Specifically, they measure physical activity, social activity, psychological activity, role functioning, and general well-being (93). Questionnaires can be self- or interviewer-administered and they can be used to determine a patient's HRQoL at a single point in time or as a longitudinal change over a period of time (94). A good HRQoL tool should consist of three characteristics. First, it should be reproducible, meaning that, in a stable situation, the patient's results should remain consistent. Second, the tool should also measure the attribute you want to measure, that is, it must be valid. Third, it should be sufficiently sensitive to detect even small, clinically significant changes in the patient's QoL (95). In practice, a good HRQoL tool is also simple, quick to complete, and provides useful clinical information. A wide range of HRQoL tools are available (1) and no tool appear superior to others (1, 96). Therefore, the choice of the measure is always based on the requirements of the research or clinical decision-making (97), and step-by-step methods for selecting an appropriate HRQoL instrument have been published (98).

2.3.1 Generic HRQoL instruments

HRQoL questionnaires can be categoried as generic or specific instruments (see Table 2). Generic instruments provide extensive information regarding a patient's physical, mental, and social health (94). They are designed to summarise the HRQoL of groups of people consisting of a wide variety of patients, diseases, injuries, cultures, and demographics. The results obtained from a generic HRQoL instrument can be presented as either a profile or an index value (that is, utility measure). For a profile measurement, the results can be presented for each dimension separately. The dimensions can also be divided into different subsections (e.g., physical, emotional, and social sections) each scored separately. At times, results are presented as one summary score (95, 99). The advantage of a profile measurement is that the HRQoL can be analysed comprehensively with

one instrument only, which saves time for both the patient and the investigator (95). However, problems with a profile measurement can arise if an improvement occurs for some HRQoL items versus decreases in others, leading to difficulties in drawing conclusions. Preference-based utility measurements are designed to integrate the HRQoL domains to produce a single index value. The general approach to assessing utility values is based on modern utility theory (100). The index value is compiled from the responses of all respondents and given a value ranging from 0 (meaning dead) to 1 (meaning completely healthy) (99). Utility measurements are used, for example, in health economics, where effectiveness is measured in terms of quality-adjusted life-years gained. Quality-weighted life-years are calculated by combining the QoL measured by a utility metric with the values across time considered (e.g., life expectancy, duration of treatment, etc.) (101, 102).

Table 2. Taxonomy of HRQoL instruments (94)

Generic instruments
Health profiles
Utility measures
Specific instruments
Disease-specific
Population-specific
Function-specific
Condition- or problem-specific

Some generic HRQoL instruments, such as the 15D, EuroQol five dimensions (EQ-5D) questionairre, and Health Utilities Index (HUI), provide both a profile and an index value (103-105). Commonly used generic HRQoL instruments in the field of rhinology have relied on the 36-item short-form survey (SF-36), HUI, EQ-5D, and the Glasgow Benefit Inventory (GBI, not to be confused with the General Behaviour Inventory, also GBI). The 15D has also been used in many rhinologic studies (see Table 3) (106-112).

Table 3. Generic HRQoL instruments used in rhinology studies (1, 108, 111-113)

	SF-36	HUI	EQ-5D	GBI	15D
Domains	36	8	5	18	15
Index number	Yes (in SF-6D, derived from the SF-36)	Yes	Yes	No	Yes
Use	Most used instrument in rhinology	Most suitable for otologic conditions	Most used instrument in health economic evaluation studies	Mainly used for surgical studies	Widely used, especially in Finland
Limitations		Lack of sensitivity for rhinologic diseases		Once-only questionnaire, no baseline data available	

2.3.2 Specific HRQoL instruments

Specific instruments are used to assess the characteristics of particular people of interest (94). The focus of a survey may lie on a specific illness (e.g., rhinitis or asthma), a specific population (based on their sex or age), a specific function (the ability to work or social functioning), or a specific condition or problem (hyposmia or pain) (see Table 2) (95). Typically, these surveys focus on a particular disease or range of symptoms. Disease-specific instruments have been developed for a wide range of disease groups, such as different ear, nose, and throat patients [77–80], asthmatics [81], and patients with obstructive sleep apnoea (OSA) [82]. Numerous disease-specific instruments exclusively apply to rhinologic patients, which Hopkins summarised in terms of their reliability, validity, responsiveness, and ease of use in a 2009 review (112). The benefits of disease-specific measures lie, in part, in their specificity in measuring the frequency and severity of specific symptoms, such as nasal congestion in CRS (114) or nocturnal awakenings in OSA [82].

2.3.3 Comparison of generic and disease-specific HRQoL instruments

The advantage of generic instruments is that they allow comparisons of HRQoL across different patient groups, whilst disease-specific instruments tend to carry a higher sensitivity to smaller, clinically important changes and are best-suited for clinical follow-up [2, 69, 78–81]. Although disease-specific instruments are often used in clinical trials, there is also some evidence that generic instruments can provide consistent or even more valid results. In a study amongst obese hospitalised patients, researchers compared two disease-specific instruments to two generic instruments, finding that the former showed no clear superiorirty in performance compared to the latter (115). Similar results

were obtained from a study of chronic obstructive pulmonary disease (COPD) patients (116), patients with systemic lupus erythematosus (117), and patients with rheumatoid arthritis (118). In two studies comparing disease-specific and generic HRQoL instruments amongst patients with asthma and schizophrenia, the generic HRQoL tools were even more valid than the disease-specific tools used (119, 120). Instruments can also reflect somewhat different characteristics of patient HRQoL, as found in a study amongst Parkinson patients, where the generic questionnaire appeared more appropriate to nonmotor symptoms whilst a disease-specific questionnaire was more appropriate for motor symptoms (121). Thus, it is important to understand that no instrument is completely reliable and researchers should possess the knowledge and skills necessary to select a valid instrument for the issue under investigation. For example, in longitudinal studies, a shorter questionnaire might be more appropriate, whilst in cross-sectional studies questionnaires can be longer such that not all items are relevant to all patients (97, 98). Since instruments produce partially different results, some suggest that generic and disease-specific HRQoL instruments should be used together. In such cases, HRQoL can be examined as extensively as possible and probably provide the most comprehensive summary of a patient's current situation (2, 3, 122, 123).

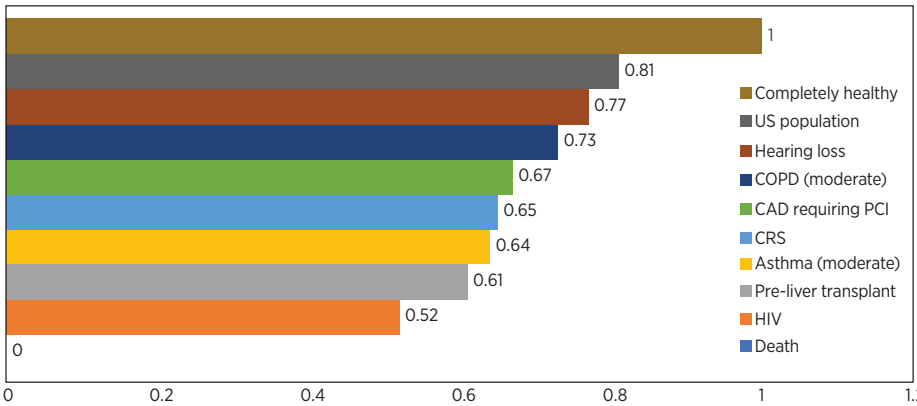
2.4 Rhinologic Diseases

Rhinologic diseases are rather common, consisting of tens of different diagnoses. The most common rhinologic diseases are allergic rhinitis (AR) affecting 10–40% of the population (6, 124), CRS affecting 5–12% of the population (8, 9), and acute rhinosinusitis (ARS) with a one-year prevalence of 6–18% (9, 10). The five most common rhinologic diseases diagnosed in the Department of Otorhinolaryngology – Head and Neck Surgery at Helsinki University Hospital (HUS) in 2019 were chronic rhinitis, chronic rhinosinusitis without nasal polyps (CRSsNP), epistaxis, chronic rhinosinusitis with nasal polyps (CRSwNP), and ARS. The prevalence of the most common rhinologic diseases are relatively high when compared to, for example, public diseases such as diabetes or asthma, and compared with the prevalence of diabetes amongst adults in Europe, which is on average 6.2% (125) and with an asthma prevalence of 8.2% (126). Related to the prevalence of rhinologic diseases, their costs to society are significant. Specifically, illness consists of both direct (outpatient physician visits, medication, and surgical treatment) and indirect (sick leave and an impaired ability to work) costs. CRS alone is estimated to result in annual costs in the US of US$22–64.5 billion (11, 127, 128). By comparison, the total annual cost of asthma in the US reaches US$81.9 billion (12), whilst diabetes reaches as as high as US$327.2 billion (129).

2.4.1 HRQoL in rhinologic diseases

The financial burden of rhinologic diseases is high, although the impact on patient HRQoL is particularly significant. The HRQoL impairment of rhinologic patients has primarily been studied amongst CRS, ARS, and AR patients. Several publications have focused on the HRQoL of patients with CRS. For instance, DeConde et al. published a review article in 2016 in which they compared a general HRQoL measurement, the short-form six dimension (SF-6D) survey, scores for CRS and other medical conditions. The mean utility value for subjects with CRS (0.65) was lower than that of subjects with moderate COPD (0.73) and amongst patients with coronary artery disease (CAD) requiring percutaneous intervention (0.67; see Figure 1). They also highlighted that the utility score of CRS patients was particularly low given the relatively young cohort of patients (mean age, 47.8 years) (17). Amongst CRS patients, the most affected domains in the HRQoL appeared to be general health-related issues — that is, sleep, mood, cognition, and productivity (17). Previous studies have demonstrated that CRS can affect patients' sleep at a similar magnitude as a sleep disorder, impairing HRQoL (130, 131). Furthermore, in a review article from 2019 by Klonaris et al., CRS patients reported a diminished QoL in several HRQoL domains, whereby the significance was most pronounced for emotional functioning, general health, physical functioning, female gender, being elderly, and highly educated patients (132). The low HRQoL amongst CRS patients might be partly explained by frequent comorbidities. Patients with CRSwNP, for example, appear to have a remarkably high prevalence of confirmed asthma, approaching 50% (19). In a study of CRS patients undergoing endoscopic sinus surgery (ESS), 64.7% of patients were diagnosed with OSA (20). Finally, in a systematic review article amongst CRS patients, the prevalence of depression reached 11–40%, with depression markedly associated with diminished CRS-specific QoL (133). Depression in CRS patients is more common if a patient suffers from significant sleep problems, olfactory dysfunction, or pain (22).

Figure 1. SF-6D scores for patients with CRS and other medical conditions (modified from DeConde et al. (17))



Abbreviations: SF-6D, short-form six dimensions survey; CRS, chronic rhinosinusitis; COPD, chronic obstructive pulmonary disease; CAD, coronary artery disease; PCI, percutaneous coronary intervention.

QoL studies amongst ARS patients remain scarce. Whilst ARS also appears to diminish patients' HRQoL statistically significantly (134, 135), it improves markedly and within a short time amongst patients receiving effective treatment (135). AR impairs patients' QoL, and perennial allergic rhinitis appears to carry a greater impact than seasonal allergic rhinitis (136). In a large study completed in the Middle East, patients with AR reported significantly lower mean EQ-5D scores than the general population (0.78 vs. 0.90, $p < 0.0001$). Additionally, comorbidities played a major role in outcomes amongst AR patients, specifically in relation to respiratory disease and COPD, which carried the highest negative impact on QoL (137).

Contradictory HRQoL results have been reported for patients with a septal deviation. In one study, their preoperative QoL was slightly better than that amongst the age- and gender-standardised control population (138), with other studies reporting the opposite (139, 140). To conclude, studies of HRQoL in other rhinologic diseases remain exceptionally scarce.

2.5 Climate and Health

Climate and weather affect human health. Changes in extreme weather conditions (unusual, severe, or unseasonal weather) in particular affect our environment (141). Climatic factors that impact our health vary, ranging from temperature, air pollution taking the forms of nitrogen dioxide levels and ozone depletion, pollen levels, and humidity (142). Heat, extreme weather events, emerging infections, and food safety have been reported as crucial climate change–related

factors influencing health outcomes (143). The impact of climate change on respiratory allergies is also important. Furthermore, climate change increases the atmospheric pollen concentration in several ways, not least by extending the pollen season (144, 145). In addition, climate change will continue to affect the health of Finns in multiple ways, although in Finland such adverse effects are diminished by a developed healthcare system and a favourable climate (e.g., less extreme weather conditions) (146).

2.5.1 Seasonal variation in difference diseases

The four seasons impact patient health in varying ways. Seasonal variation associates with the incidence, severity, exacerbation, and even mortality of many diseases. For example, the incidence of tuberculosis peaks during spring (23), whilst global suicide rates follow a similar cyclical pattern and are highest during spring (24). In two studies of adult acute appendicitis, incidence decreases during the winter months (26, 147). The disease severity may also vary with the season, as reported, for example, in restless leg syndrome (27), sleep-disordered breathing in children (28), and bipolar disorder (29). A clear seasonal variation of symptoms also exists amongst asthma patients. Respiratory pathogens, such as rhinovirus and influenza, complicate symptoms during winter (30, 31) and pollen, specifically tree pollen, during spring and summer (32, 33). Amongst patients with allergic diseases, the seasonal variation of symptomsis is, of course, common.

Moreover, overall mortality appears highest during the winter months, especially amongst the elderly (34, 35), whilst prolonged cold periods, particularly during cold spells, have been associated with increased mortality (36). In addition to cold spells, daily and hourly temperature variability (TV) also appears related to an increased all-cause and cardiorespiratory mortality risk. In a large meta-analysis, a 1°C increase in the daily TV associated with an increase of 0.53% in cardiovascular mortality risks and a 0.62% increase in respiratory mortality risks (37).

Environmental factors affecting rhinologic patients consist of indoor and outdoor temperatures, relative and absolute air humidity levels, allergens, and air pollutants (148), whilst seasonality has also been linked to rhinologic diseases. Epistaxis occurs more frequently during the cold and dry winter months (38). Danielides et al. examined the association of different meteorological parameters with acute laryngitis and Bell's palsy. The peak frequency of acute laryngitis associated with winter weather conditions. By contrast, in Bell's palsy, no seasonality was detected in the incidence of disease (149, 150). In a study examining the Australian climate, incidental sinus magnetic resonance imaging (MRI) abnormalities were found in 65.2% of study patients in winter compared with 50.6% during summer, a statistically significant difference (151).

Prior research on the seasonal variation of CRS focused primarily on acute exacerbations of CRS, which appear to occur more frequently in winter and spring (39, 40). One likely explanation for this is that viral infections in winter and pollen in spring aggravate the symptoms as in asthmatic patients (40).

2.5.2 Seasonal variation in HRQoL

Studies regarding the seasonality of HRQoL remain scarce. A large population-based study of HRQoL amongst the US adult population revealed that the worst physical health occurred during winter and the best occurred during summer. Mental health, however, was worst during spring and autumn, although the seasonal effect was much smaller. Since the season impacts patient HRQoL, researchers are encouraged to take into account seasonality effects when comparing data from different studies (41). In a Finnish population study, HRQoL was strongly influenced by both indoor lighting and seasonal changes in mood and behaviour (42). In addition, CRS patients appear to experience seasonal variation in disease-specific HRQoL, appearing more symptomatic during winter months, the variation of which may also be primarily explained by a depressed mood (43).

2.6 Rhinologic Patients and Work

2.6.1 Occupational exposure

The nasal mucosa serves as the gateway to the body and most airway stimuli pass through it. Many occupational exposures, such as chemicals, gases, and organic dusts, associate with airway symptoms resulting from mucosal inflammation (152). Occupational sensitisers cause occupational asthma (OA) (49, 153), rhinitis (OR) (154), and CRS (57). In addition to the occupational exposures that can cause a variety of respiratory diseases, they can also exacerbate existing ones (44, 45). The European Union (EU) published a list of hazardous substances, including respiratory sensitisers, manufactured and imported to Europe, known as the EU Annex, which includes more than 400 agents documented to act as occupational respiratory sensitisers (155).

2.6.2 Occupatonal respiratory sensitisers and irritants

Occupational respiratory sensitisers fall into two groups according their molecular weight. Most common agents consist of large high molecular weight sensitisers (HMWs, >5 kD), which include allergens such as animal proteins, flour, and plants. Low molecular weight sensitisers (LMWs) consist, by

contrast, of chemicals, wood dust, and drugs (46, 153). Table 4 summarises the categorisation of occupational respiratory sensitisers.

Table 4. Occupational respiratory sensitisers (modified from Tiotiu et al. (46))

HMW agents	LMW agents
Flour, cereal	Chemicals
Latex	Drugs
Animals	Wood dust
Enzymes	Metals
Insects	
Fungi	
Vegetable gums	

Abbreviations: HMW, high molecular weight; LMW, low molecular weight.

When inhaled, HMW can sensitise a person and cause an immunoglobulin E (IgE) mediated-type 1 hypersensitivity reaction, where histamine and other antibodies such as leukotrienes, prostaglandin, and cytokines are released from mast cells and basophils (154, 156, 157). This cascade ultimately leads to the clinical expression of disease. LMW, by contrast, can cause rhinologic symptoms in two ways: via IgE-mediated reactions or by causing airway inflammation via mechanisms which remain poorly understood (152, 158). Respiratory sensitisers cause upper-airway symptoms including sneezing, a blocked nose, rhinorrhoea, or itchiness. They can also cause symptoms mimicking rhinosinusitis such as facial pain and hyposmia (152).

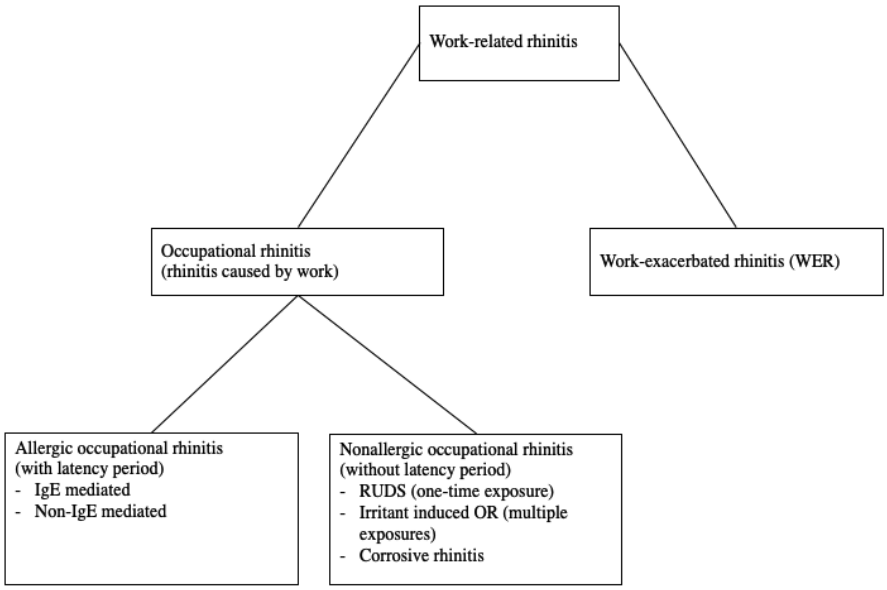
2.6.3 Occupational rhinitis and rhinosinusitis

Occupational rhinitis is defined as 'an inflammatory disease of the nose, which is characterised by intermittent or persistent symptoms (i.e., nasal congestion, sneezing, rhinorrhoea, and itching), and/or a variable nasal airflow limitation and/or hypersecretion due to causes and conditions attributable to a particular work environment and not to stimuli encountered outside the workplace' (154). OR is estimated as 2–4 times more common than occupational asthma (54), although occupational asthma garners much greater interest amongst both clinicians and researchers (50). The overall prevalence and incidence of OR are unknown, whilst wide variation exists between different occupational groups. In a review article by Siracusa et al., the prevalence of OR in various working populations exposed to HMW and LMW agents varied from 2% to 87% (50). The prevalence of OR is particularly high amongst furriers, bakers, hair dressers, farmers, and veterinarians (51-53). In addition, OR associates with an increased risk for the development of OA (159) and up to 92% of OA patients

report symptoms of OR (50). Moreover, OR significantly impacts patient QoL and work efficiency. Yet, the general HRQoL amongst OR patients compared with rhinitis unrelated to work is substantially lower (160, 161).

The classification of occupational rhinitis has shifted over time. Currently, the term work-related rhinitis (WRR) should be used as a superscript, with the subcategories of occupational rhinitis distinguished according to the underlying pathomechanisms and clinical manifestations (Figure 2) (53, 162). An allergic form of occupational rhinitis can occur if a worker experiences repeated exposure to workplace sensitisers over a long period of time. A nonallergic form, by contrast, can occur following a single exposure to high concentrations of an irritant, classified as reactive upper respiratory distress syndrome (RUDS). Irritant-induced OR occurs when a patient is repeatedly exposed to irritants. Finally, a third form of nonallergic OR manifests as corrosive rhinitis, which appears as a persistent inflammation of the nasal mucosa or as ulcers. Chlorine and ammonia, for example, are known as causative agents of corrosive rhinitis (53, 152, 163, 164).

Figure 2. The classification of occupational rhinitis (154)



Abbreviations: WER, work-exacerbated rhinitis; IgE, immunoglobulin E; RUDS, reactive upper respiratory distress syndrome; OR, occupational rhinitis.

Occupational exposures have primarily been examined amongst rhinitis patients, although the relationship between chronic rhinosinusitis and occupational exposure has only been established in a few studies (55-58). In a large (n = 7952) prospective population-based study in Norway, the five-year incidence of CRS was 5.5%, with exposure to various occupational-specific irritants

associating with new-onset CRS. In particular, hair-care products, super glue, strong acids, cooking fumes, and wood dust significantly associated with the risk of developing CRS (57).

2.6.4 Workplace absenteeism

Self-reported sickness absences per employed person in Finland stood at 9.1 days in 2020, remaining moderately stable over the past 15 years, varying from 8.5 to 10.1 days per year (13).

On average, 50% of sickness absence days result from musculoskeletal and mental diseases, with a high prevalence of these diagnoses also observed in other European countries as well (13, 165-168). Sick leave amongst rhinologic patients has been studied amongst some diagnostic groups. CRS has been associated with an average loss of 8–14 work days (14) and AR with 0.60–9.9 work days per year (15, 16). Endoscopic sinus surgery carries a remarkable role on sickness absences due to rhinosinusitis in CRS patients. Specifically, sick leave dropped from 8–14 days to 1–7 days 12 months after surgery (169). CRS appears to increase chronic school absenteeism in children and young adults, with an average of 4.6 school days per year missed because of illness (170). In a population-based work-force study, WRR patients did not report higher sickness absence rates than non-WRR patients and controls, although WRR associated with a significantly higher rate of impaired performance at work (i.e., presenteeism) (161). In a literature search of sick leave amongst patients with other rhinologic diseases, no publications were found.

3 AIMS OF THE STUDY

The purpose of this research was to study the general and disease-specific HRQoL amongst patients with different rhinologic diseases.

The specific aims of this study were as follows:

1. To compare the general HRQoL of rhinologic patients to the age- and sex-standardised general population and to patients with other diseases.
2. To evaluate the seasonality of HRQoL of rhinologic patients.
3. To survey the HRQoL and subjective symptoms of rhinologic patients at work, to analyse the relevant irritant exposures at work, and to determine the correlation between symptoms and exposure. We also aimed to study the median sick leave of rhinologic patients due to rhinologic diseases.
4. To study whether the 15D HRQoL instrument can be transformed into an electronic version without compromising its reliability and validity. In addition, we aimed to evaluate the preference amongst patients for different versions of the questionnaire.

4 MATERIALS AND METHODS

All of the study patients were diagnosed and treated in the Department of Otorhinolaryngology — Head and Neck Surgery at HUS, a large referral department providing secondary and tertiary ear, nose, and throat healthcare services to over 1.6 million inhabitants (29% of the Finnish population) in southern Finland (171).

4.1 Studies I–III

We designed a cross-sectional, questionnaire-based study to collect data on HRQoL amongst patients with different rhinologic diseases or symptoms. All adult (≥18 years old) patients referred to the Department of Otorhinolaryngology due to a rhinologic disease or symptoms within the study months (February, May, August, and November) in 2014 were invited to participate. We also collected a small subset of preliminary data in August and November 2013. All patients received via post a medical history questionnaire and a generic HRQoL questionnaire (15D). One question ('Do you have physician-diagnosed asthma?') was added to the questionnaires during the recruitment period. We asked patients to complete the surveys within three days of receipt and patients returned the questionnaires via post or during an outpatient visit. We excluded patients seen during emergency room visits. We also collected International Classification of Diseases, tenth revision (ICD-10) data following outpatient visits from the electronic patient record system. The primary diagnosis of the patient we considered was the diagnosis requiring active treatment. For comparisons, we used age- and sex-matched 15D data from a sample of the population (n = 1329) from the same hospital district area (172). All patients who participated in the study were examined in the rhinologic clinic at HUS and their diagnoses were based on international guidelines.

4.1.1 Study II

The study periods for study II were as follows: 1 February through 15 March (February); 1 May through 15 June (May); 1 August through 15 September (August), and 1 November through 15 December (November). We excluded patients whose forms were completed at times outside these periods. Patients also completed the disease-specific Sino-Nasal Outcome Test 22 (SNOT-22)

questionnaire. Climate data were provided by the Finnish Meteorological Institute (FMI).

4.1.2 STUDY III

In study III, we recruited patients in May, August, and November 2014, excluding patients who had not worked or studied full-time during the preceding six months. In addition to the forms previously mentioned in studies I and II, study patients received an open-ended survey via post focused on their work tasks, current work status, patient-evaluated exposures to different indoor environmental triggers, and their current job title. Patients were also asked to report whether they experienced a worsening of nasal symptoms resulting from any work-related indoor environmental exposures. A specialised occupational hygienist from the Finnish Institute of Occupational Health used patient job titles, work descriptions, and patient-reported types of exposures to determine whether a patient was exposed to specific occupational sensitisers or irritants. Using the basic occupational hygiene safety principle, patients were assessed as exposed in cases appearing uncertain. Patients were also asked to report their need for sick leave during the previous year.

Work categorisation

We classified patients' socioeconomic status using Statistics Finland's 1989 classification (173). We used patients' work titles and job descriptions to categorise different work groups, relying on the International Standard Classification of Occupations (ISCO-08, (174)). When comparing our patient sample to the entire Finnish and Uusimaa district employed population, we used the 2014 Statistics Finland's Classification of Socioeconomic Groups (n = 2 217 049 and n = 722 266) (175).

4.2 STUDY IV

Study IV was conducted in April through June 2019. Here, we invited rhinologic and otological patients waiting for their appointment in the Department of Otorhinolaryngology to participate. The inclusion criteria were as follow: the patient should be an adult (≥18 years old), Finnish-speaking, and possess a mobile phone suitable for use with the BuddyCare application used in this study (iOS or Android).

Study patients were divided into four groups of equal size, each of which completed both a paper 15D form and either a browser-based or mobile application–based 15D form.

The first form was completed before the outpatient visit and the second form was completed following it within three days of the visit. Patients were provided printed instructions on how to download the application. After completing the second 15D questionnaire, patients were asked to complete another questionnaire on the acceptability and reliability of the forms.

Buddycare

Buddy Healthcare Ltd Oy offers healthcare organisers different pathways to, for example, evaluate and follow patient health status. For our study, Buddy Healthcare provided the mobile application and the platform for the web-based form, although Buddy Healthcare did not otherwise act as a sponsor of our study (176).

4.3 HRQoL Instruments

4.3.1 15D

The 15D is a generic, standardised 15-dimension HRQoL measurement tool which can be used both as a profile and single-index score measure. The dimensions of the instrument are as follows: moving, seeing, hearing, breathing, sleeping, eating, speech, excretion, normal activities, mental functioning, discomfort and symptoms, depression, distress, vitality, and sexual activity. For each dimension, the respondent chooses one of the five levels that best describes thier state of health at that moment (1 indicates the best level, whilst 5 indicates the worst). If there are no more than three missing answers along the 15D dimensions, missing scores can be predicted using linear regression modelling based on age, gender, and answers to the other dimensions, which serve as independent variables. The validation of the instrument is based on the application of multi-attribute utility theory. A set of utilities or preference weights elicited from the general public through a three-stage valuation procedure provides an additive aggregation formula to generate the utility score — that is, the 15D score (single-index number) across all dimensions. The maximum score is 1 (no problems on any dimension) and the minimum score is 0 (equivalent to being dead) (103). The minimal clinically important difference (MCID) — that is, the smallest change that can be detected by a patient — is ±0.015 for the 15D scores (177).

15D is a sensitive instrument, and capable of detecting cross-sectional differences and changes over time in HRQoL. When comparing it to other similar generic QoL instruments, 15D is at least equally good or even better for some segments (e.g., in structural validity and sensitivity) (178-181). In addition, 15D has been employed in hundreds of studies as well as in various studies

amongst rhinologic patients (110, 123, 138, 139, 182). An electronic version of 15D is already in use in many institutions (https://www.apotti.fi/en/, https://bcbmedical.com/, https://www.checkware.com/, and https://stellarq.com). However, the implementation of an electronic version of 15D has not yet been validated and no data from patient experiences or response rates (RRs) are available.

4.3.2 Sino-Nasal Outcome Test 22 (SNOT-22)

The Sino-Nasal Outcome Test 22 (SNOT-22) is a disease-specific rhinologic HRQoL instrument validated in 2009 (114). Modified in 2006 from its previous version, SNOT-20, two additional items were identified as important: nasal obstruction and problems with smell/taste (114, 183). SNOT-20 is derived from the former Rhinosinusitis Outcomes Measure 31 (RSOM-31) (184, 185). SNOT-22 contains 22 questions related to sinonasal symptoms and QoL. In the questionnaire, patients rate each item from 0 to 5 (0 indicating no problem, 1 a very mild problem, 2 a mild problem, 3 a moderate problem, 4 a severe problem, or 5 a problem as bad as it can be). The total maximum score for SNOT-22 is, thus, 110 points. MCID has been reported at 8.9 (114), although in a recent multi-institutional study its value was somewhat higher, at 12, amongst chronic rhinosinusitis (CRS) patients (186). SNOT-22 has also been evaluated in several populations of healthy subjects, with the mean taken as a normal score, ranging from 9.8 to 12.8 (114, 187-189). In 2006, Morley et al. analysed 15 different disease-specific sinonasal outcome tests for CRS, whereby SNOT-22 emerged as the most suitable due to its reliability, validity, and responsiveness (190). Moreover, SNOT-22 has been validated in various languages (191-196) including Finnish (187, 197).

SNOT-22 was originally validated only amongst CRS patients (114), whilst its use for AR is now also established (198). Nevertheless, the SNOT-22 instrument has been used in many studies amongst rhinologic patients, particularly during follow-up after a surgical procedure such as septoplasty (107, 138, 199, 200), turbinoplasty (201, 202), ESS (107, 203-205), laser treatment for epistaxis in tele-angectasia (206), and endoscopic sinonasal and skull-base tumour resection (207-210). SNOT-22 has also been used amongst patients with a septal perforation (211, 212), cystic fibrosis with sinonasal involvement (213), and in patients with COVID-19 (214-217).

SNOT-22 subscales

Once the use of the SNOT-22 instrument was established in clinical settings and research studies, it found use alongside surgical interventions such as ESS, impacting various dimensions of the survey in distinct ways (218). Because of this, SNOT-22 can be particularly useful when divided into subscales (219). As

such, several different subscales have been published, with all following roughly the same division: rhinologic symptoms, otological symptoms, items related to sleep, and finally, psychological issues (219-222). When using the SNOT-22 subscales, a problem arises from the lack of consensus on which division to use. However, this will hopefully change in future. In fact, last year, validated subscales for CRSwNP were published (223).

4.4 Statistical Analyses

In studies I and III, we used the student's independent samples t-test to compare the means between two groups. If the requirement for a normal distribution was not satisfied, we employed the Mann–Whitney U-test.

In study II, we used the analysis of variance (ANOVA) when comparing population means. When the requirement for a normal distribution was not met, we relied on the Kruskal–Wallis one-way ANOVA. The D'Agostine omnibus test of normality was used to determine the normality and equal variance assumptions and Brown–Forsythe test of homogeneity, respectively. To achieve data normality, power transformations were used when appropriate prior to statistical analysis.

In study IV, we used the Shapiro–Wilk's test to examine the data normality. We calculated the statistical analysis of equivalence using the two-way, mixed-effect intraclass correlation coefficient (ICC), comparing the mean and median 15D scores and weighted kappa for item scores. The paired samples t-test and Wilcoxon signed-rank test were used when the means and medians were compared from different time points. The Pearson's chi-squared test was used to evaluate preferences and the weighted kappa was defined linearly.

In studies I–III, all statistical analyses were performed using NCSS 12 Statistical Software (2018) (NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/ncss). In study IV, we used SPSS version 25 (IBM SPSS, Chicago, USA) for statistical analyses.

The differences between groups were considered statistically significant at the level of $p < 0.05$.

4.5 Ethics

The Research Ethics Board of HUS approved the study protocols (Dnro 336/13/03/00/13 and Dnro HUS/3066/2018). We obtained written informed consent from all study subjects.

5 RESULTS

5.1 Study Recruitment and Demographic Characteristics (Studies I–III)

We recruited study patients in February, May, August, and November 2014 (studies I–II) and May, August, and November 2014 (study III). In addition, a small preliminary dataset was collected in August and November 2013 (studies I-III). Altogether, 349 (studies I–II) and 224 (study III) patients, respectively, responded to the questionnaires. We recorded the RR during an one-month period (November 2014), which reached 46.3%. We found no statistically significant age or sex differences between respondents (mean age 48.6 years, 47.2% male) and nonrespondents (mean age 44.1 years, 46.0% male). A flowchart of the participant recruitment appears in Figure 3. Table summarises the patient characteristics and primary diagnoses in studies I–III.

Figure 3. Flowchart of participant recruitment

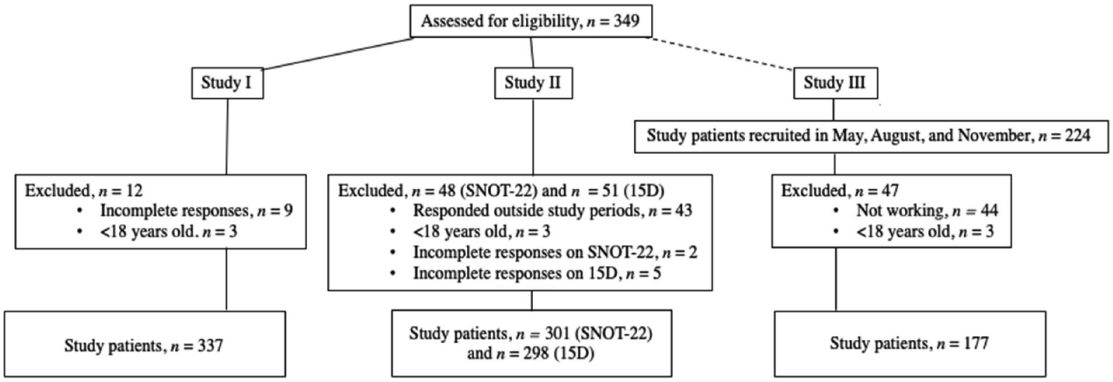


Table 5. Characteristics of study patients (studies I–III)

Characteristics	Study I	Study II		Study III
		SNOT-22	15D	
All patients, *n*	337	301	298	177
Age, in years				
Mean	50.2	50.5	50.5	44.8
Range	18–85	NA	NA	18.5–75.1
Gender, *n* (%)				
Male	170 (50.4)	147 (48.8)		84 (47.4)
Female	167 (49.6)	154 (51.2)		93 (52.6)
Smoking				
No	166 (49)	NA		92 (52.3)
Yes	47 (14)	NA		27 (15.3)
Quit	121 (36)	NA		57 (32.4)
Missing data	3 (0.9)	NA		NA
Sleep apnoea				
No	304 (90)	NA		NA
Yes	33 (10)	NA		NA
Main disease groups				
CRS	121 (36)	105 (35)		59 (33)
CRSsNP	73 (22)	63 (21)		38 (21)
CRSwNP	48 (14)	42 (14)		21 (12)
Rhinitis	106 (31)	97 (32)		62 (35)
NAR	62 (18)	59 (20)		51 (29)
AR	44 (13)	38 (13)		11 (6)
Septal deviation	35 (10)	30 (10)		22 (12)
Others	75 (22)	69 (23)		34 (19)

Abbreviations: SNOT-22, Sino-Nasal Outcome Test 22; 15D, 15 dimension health-related quality of life instrument; NA, data not available; CRS, chronic rhinosinusitis; CRSsNP, chronic rhinosinusitis without nasal polyps; CRSwNP, chronic rhinosinusitis with nasal polyps; NAR, nonallergic rhinitis; AR, allergic rhinitis.

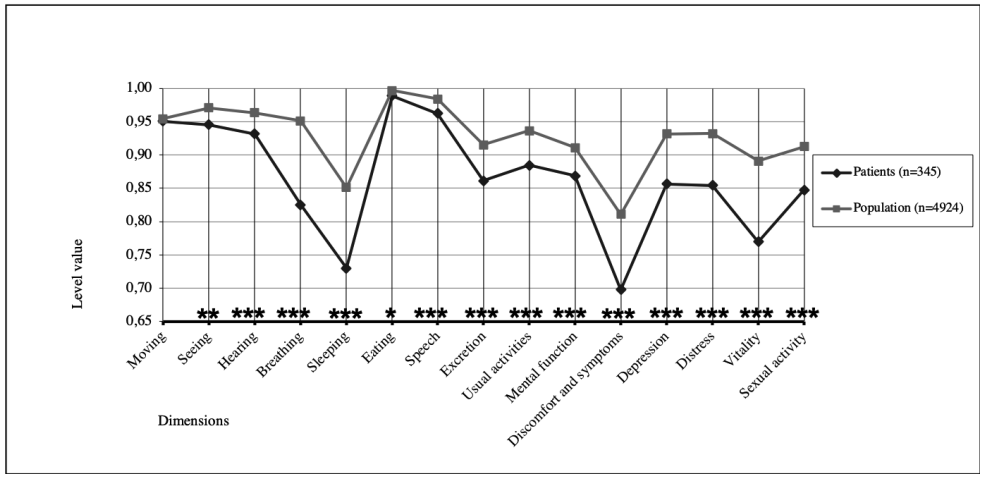
5.2 Generic HRQoL of Rhinologic Patients (Study I)

Amongst 337 rhinologic patients, we found no difference in the mean 15D score comparing men and women ($p = 0.549$) nor between never smokers, patients who quit smoking, and current smokers ($p = 0.309$). Only 128 patients answered the question regarding asthma since it was added to the questionnaires in May 2014. Amongst these, 25 (19.4%) reported having asthma. We detected no difference in the mean 15D score between asthmatic and nonasthmatic patients ($p = 0.982$).

The mean 15D scores for the mean dimension level values across five common rhinologic disease groups standardised for age also did not differ statistically significantly.

When we compared the mean (±standard deviation, SD) 15D scores for patients (0.865 [±0.101]) to that of the age- and sex-standardised general population (0.929 [±0.023]), we detected a statistically significant difference ($p < 0.001$), which was clinically important. Patients faired poorer on all 15 dimensions except for moving when compared with the general population (Figure 4). In particular, sleep, discomfort and symptoms, vitality, and breathing were affected amongst these patients.

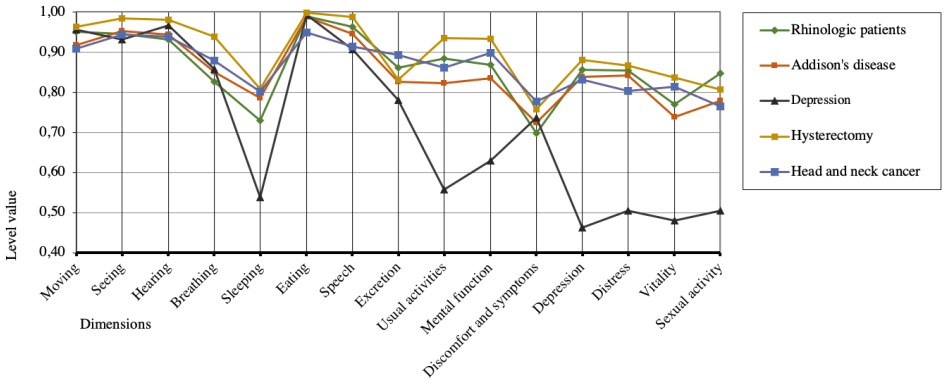
Figure 4. Comparison of 15D profiles for rhinologic patients versus the age- and sex-standardised general population



*$p < 0.05$
**$p < 0.01$
***$p < 0.001$

We also compared the mean 15D scores amongst rhinologic patients versus the scores from patients in other disease groups from the same hospital district (Figure 5) (224-227). These groups were not weighted to reflect the age and sex distribution of the rhinologic patients. The mean (±SD) 15D score was lowest for depression (0.729 [±0.120]), followed by Addison's disease (0.853 [±0.122]), rhinologic patients (0.865 [±0.101]), head and neck cancer patients (0.872 [±0.104]), and hysterectomy patients (0.907 [±0.071]).

Figure 5. 15D profiles of rhinologic patients and patients with Addison's disease (n = 107, mean age 50 years, 20% men), depression (n = 89, mean age 40 years, 41% men), hysterectomy (n = 337, mean age 53 years), and head and neck cancer (n = 214, mean age 63 years, 66% men)



Diagnosed OSA was identified in 10.5% of rhinologic patients. Patients who had a rhinologic disease and OSA scored clinically and significantly poorer than rhinologic patients without an OSA diagnosis. The mean 15D (±SD) scores were 0.816 (±0.103) and 0.871 (±0.099), respectively, (p = 0.002). However, rhinologic patients scored poorer than the general population regardless of OSA (mean 15D score for rhinologic patients without OSA was 0.871, and for the general population was 0.929; $p < 0.001$.)

5.3 Seasonality of HRQoL amongst Rhinologic Patients (Study II)

In this study, we recruited 301 patients (Table 5). Three did not complete the 15D questionaire and were excluded from further analyses. The mean (±SD) 15D scores were 0.865 (±0.096) in February, 0.860 (±0.102) in May, 0.865 (±0.114) in August, and 0.868 (±0.097) in November. We observed no differences between groups (p = 0.968), and no significant differences emerged in the 15D dimensions for the different study periods (p = 0.149–0.936). The mean SNOT-22 values were 41.0 (n = 72, ±SD 19.8) in February, 37.0 (n = 78, ±SD 17.5) in May, 36.4 (n = 65, ±SD 19.3) in August, and 36.0 (n = 86, ±SD 18.1) in November.

We found no statistically significant differences between the mean SNOT-22 values across the study months (p = 0.385). The mean values for the SNOT-22 question subscales varied, but we found no statistically significant seasonal variation across the subscales either.

The mean temperatures and mean absolute humidity for the study periods recorded at the Helsinki–Kaisaniemi weather station in 2014 are summarised in Table 6.

Table 6. Climate statistics recorded at the Helsinki–Kaisaniemi weather station during the study periods in 2014

	Tmean (°C)	ΔTmean (°C)	Tmax_avg (°C)	ΔTmax (°C)	Tmin_avg (°C)	ΔTmin (°C)	Rel Hum – mean (%)	Abs Hum – mean (g/m³)
Feb 1 – Mar 15	1.0	+4.9	2.7	+3.9	-0.5	+6.2	90	4.7
May 1 – Jun 15	12.1	+0.8	16.2	+0.7	8.6	+1.1	79	8.7
Aug 1 – Sept 15	16.9	+1.7	20.7	+2.2	13.6	+1.6	83	11.9
Nov 1 – Dec 15	3.0	+2.2	4.5	+1.6	1.5	+2.9	91	5.5

Abbreviations: Tmean, mean temperature; ΔTmean, deviation of the mean temperature from the climate normal (1981–2010); Tmax_avg, daily maximum temperature on average; ΔTmax, deviation of the maximum temperature from normal; Tmin, daily minimum temperature on average; ΔTmin, deviation of the minimum temperature from normal, Rel Hum, relative humidity; Abs Hum, absolute humidity.

5.4 Rhinologic Symptoms and HRQoL at Work (Study III)

All 177 study patients accurately represented the age, gender, and socioeconomic status of the Finnish labour force in 2014 in the Uusimaa district (Table 7). But when comparing patients to the entire Finnish labour force, we observed fewer manual labourers ($p = 0.002$). Altogether, 23 (22.5%) patients reported having asthma.

Table 7. Socioeconomic status groups*

Socioeconomic group	Patients, %	Population in Uusimaa, %	Population in Finland, %
1	7.0	8.6	10.8
2	32.6	28.8	21.9
3	39.0	38.3	37.6
4	21.5	24.3	29.7

*Study patients and the general population (Finnish Labour Socioeconomic Group in 2014 in the Uusimaa district and in Finland).
Abbreviations: 1, self-employed persons (including group 1, farmers and group 2, other); 2, upper-level employees; 3, lower-level employees in administrative and clerical occupations; 4, manual labourers.

Most patients (60.1%, $n = 101$) reported that their rhinologic symptoms worsened at work, whilst 39.9% ($n = 67$) mentioned that symptoms did not worsen. We detected no gender, age, or socioeconomic status differences between patients whose symptoms worsened at work and those whose symptoms did not. The

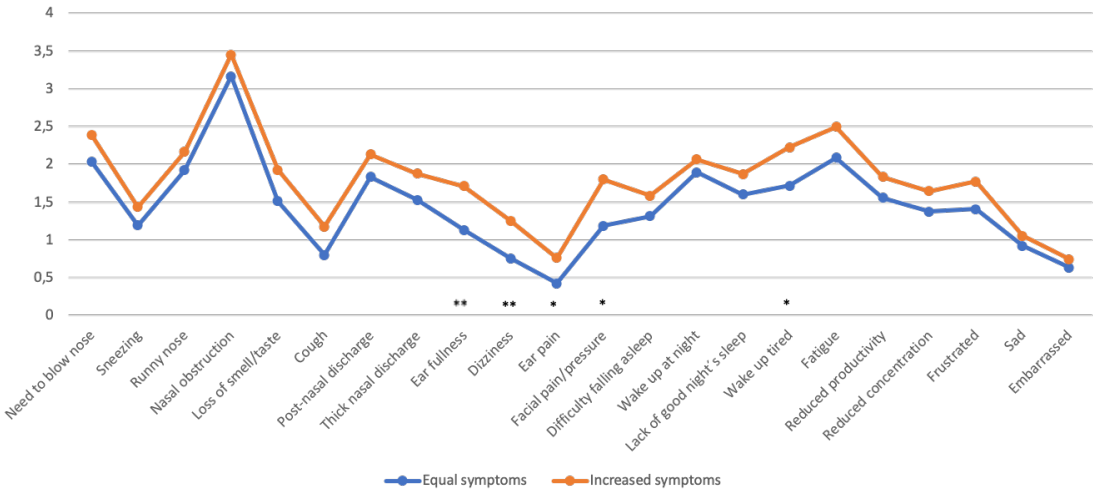
number of asthmatics, allergy patients, or smokers did not differ between these two groups.

A majority of patients (56.7%, n = 55) reporting that their rhinologic symptoms worsened in the work environment due to nonspecific dust or powdery substances, with 35.1% (n = 34) mentioning stale or mouldy air and 20.6% (n = 19) mentioning cold air. When examining the specific occupational sensitisers and irritants, 25% of patients whose symptoms worsened and 24.8% of patients whose symptoms did not worsen at work mentioned exposure to them.

The mean SNOT-22 score amongst patients with symptoms that worsened at work was significantly higher compared with scores amongst non-work-related patients (39.42 and 32.05, p = 0.0165).

There was also a statistically significant difference between these groups in the mean values of five items (Figure 6). The mean values on the SNOT-22 subscales differed significantly between these groups in terms of nasal symptoms (p = 0.029) and otological/facial pain (p = 0.00017), whereby patients whose symptoms worsened at work scored lower than those whose symptoms did not. However, the mean 15D scores did not differ between these two groups.

Figure 6. SNOT-22 profile amongst patients with worsening symptoms at work and amongst patients with consistent symptoms at work and during free time



*p < 0.05
**p < 0.01

Altogether, 43 (24.3%) patients were exposed to specific occupational agents in their workplace. More specifically, 38 patients (21.5%) were exposed to an LMW agent, 9 patients (5.1%) to an HMW agent, and 4 patients (2.3%) to both HMW and LMW agents or irritants. Interestingly, the mean SNOT-22 scores amongst exposed (37.2) and nonexposed patients (35.9) did not differ (p = 0.659). Furthermore, we observed no statistically significant difference between

exposed and nonexposed patients in the SNOT-22 subscales. The mean 15D score did not differ between the exposed and nonexposed patients (0.867 and 0.885, respectively, $p = 0.320$).

Almost three-fifths of patients reported sick leave periods due to rhinologic diseases during the previous year. The mean length of absence from work due to a rhinologic disease was 7.7 (±SD 14.6) days, and patients estimated their overall sickness absences as totaling 15.4 (±SD 25.9) days.

5.5 Converting the 15D Instrument to Electronic Formats (Study IV)

This study consists of 160 patients divided into four different groups. A flowchart of the study population appears in Figure 7 and the patient characteristics are summarised in Table 8.

Figure 7. Flowchart of study participants

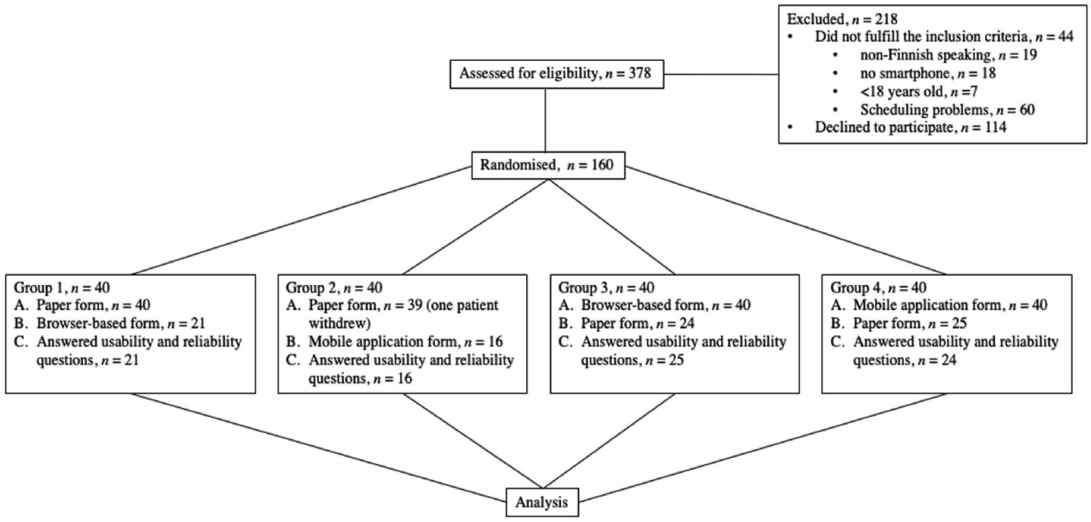


Table 8. Characteristics of patients in study IV

	All patients, n (%)		
		Two questionnaires	One questionnaire
Patients, n (%)	159	86 (54.1)	73 (45.9)
female	84 (52.8)	46 (53.5)	38 (52.1)
male	75 (47.2)	40 (46.5)	35 (47.9)
Age, in years			
range	18–81	18–80	18–81
mean ± SD	45.2 ± 15.0	48.2 ± 15.7	41.6 ± 13.5
female	44.6 ± 14.5	47.6 ± 15.2	41.0 ± 13.0
male	45.8 ± 15.7	49.0 ± 16.4	42.2 ± 14.3
Age groups, n (%)			
18–29	26 (16.4)	14 (16.3)	12 (16.4)
30–39	37 (23.3)	12 (14.0)	25 (34.2)
40–49	34 (21.4)	17 (19.8)	18 (24.7)
50–59	35 (22.0)	21 (24.4)	13 (17.8)
60–69	16 (10.1)	15 (17.4)	1 (1.37)
≥70	11 (6.9)	7 (8.1)	4 (5.48)
15D score			
median	0.940	0.942	0.935
range	0.57–1.00	0.60–1.00	0.57–1.00
mean ± SD	0.912 ± 0.083	0.911 ± 0.086	0.912 ± 0.079
female	0.912 ± 0.078	0.910 ± 0.086	0.913 ± 0.068
male	0.912 ± 0.088	0.913 ± 0.087	0.911 ± 0.091

Abbreviations: SD, standard deviation; 15D, 15 dimension generic health-related quality-of-life instrument.

All study patients returned the first questionnaire and both questionnaires were completed by 86 (54%) patients. The wash-out period was on average 1.9 days. The sex distribution on the 15D scores did not differ between those who returned only one questionnaire and those who returned both ($p = 0.857$ and $p = 0.891$). However, those who returned both forms were on average 6.6 years older than those who returned only the first form ($p = 0.005$). The mean 15D profiles and scores for patients did not differ between the first and second measurement.

Equivalence

For the measurement equivalence for the 15D index scores, we observed a high correlation between the paper and web-based formats, and a high-to-moderate correlation between the paper and mobile application questionnaires (Table 9).

Table 9. Intraclass correlation coefficients (ICCs) and exact agreement between the modes of administration

Group	n	ICC	ICC 95% CI	Exact agreement
Paper–web	21	0.910	0.79–0.96	296/315 (94%)
Paper–mobile	16	0.928	0.60–0.98	196/240 (82%)
Web–paper	25	0.935	0.86–0.97	341/375 (91%)
Mobile–paper	24	0.949	0.88–0.98	327/360 (91%)

Abbreviations: ICC, intraclass correlation coefficients; CI, confidence interval.

We calculated the mean 15D score differences in order to compare the modes of administration (Table 10). In the paper–mobile group, the mean 15D score was statistically significantly higher for the second measurement when patients completed the mobile application form (-0.029 and $p = 0.003$). However, in the mobile–paper group, we found no difference between the mean 15D scores. When estimating the ICCs, a sufficient sample size of 18 patients/random group was determined based on the methods described by Zou and Walter's research groups using the following parameters: $\alpha = 0.05$; $\beta = 0.20$; $\rho 0 = 0.70$; $\rho 1 = 0.90$; $k = 2$ (228, 229). The sample size of random group 2 fell below this recommended minimum ($n = 16$).

Table 10. The mean 15D score differences between modes of administration

Group	***n***	**Mean difference (SD)**	**MD 95% CI**	***p* value**
Paper–web	21	0.006 (±0.026)	-0.005 to 0.018	0.266
Paper–mobile	16	-0.029 (±0.033)	-0.047 to -0.012	0.003
Web–paper	25	-0.005 (±0.026)	-0.016 to 0.006	0.180
Mobile–paper	24	0.010 (±0.027)	-0.001 to 0.022	0.074

Abbreviations: 15D, 15 dimension generic health-related quality-of-life instrument; SD, standard deviation; MD, mean difference; CI, confidence interval.

Preference

The majority of patients ($n = 63$, 74.1%) preferred the electronic forms (browser-based and mobile application forms) regardless of the randomisation group, age, or gender (Table 11). Interestingly, the preference did not differ between age groups. Yet, the browser-based questionnaire was preferred over the paper form more often than the mobile application. In further analyses, we detected a statistically significant difference for two questions: patients found the electronic form faster to complete ($p = 0.002$) and their ability to modify responses was better ($p = 0.018$). In addition, the mobile application form was preferred over the paper form in terms of the possibility of revising responses ($p = 0.041$).

RRs for completing both questionnaires were lower in both groups completing electronic forms at home (41.0% for the mobile application and 52.5% for browser-based questionnaires) than in the paper form groups (60.0% and 62.5%).

Table 11. Preference for different modes of administration

	Which mode did you prefer?		
	Paper	**Electronic**	**No opinion**
Patients, n (%)	14 (16.5%)	63 (74.1%)	8 (9.4%)
Group			
Paper–web (n = 21)	1 (4.8%)	17 (81.0%)	3 (14.3%)
Paper–mobile (n = 15)	3 (0.20%)	11 (73.3%)	1 (6.7%)
Web–Paper (n = 25)	3 (12.0%)	21 (84.0%)	1 (4.0%)
Mobile–paper (n = 24)	7 (29.2%)	14 (58.3%)	3 (12.5%)
Sex			
female (n = 47)	11 (23.4%)	33 (70.2%)	3 (6.4%)
male (n = 38)	3 (7.9%)	30 (78.9%)	5 (13.2%)
Age groups			
18–29 (n = 13)	3 (23.8%)	9 (69.2%)	1 (7.7%)
30–39 (n = 12)	1 (8.3%)	10 (83.3%)	1 (8.3%)
40–49 (n = 17)	2 (11.8%)	13 (76.5%)	2 (11.8%)
50–59 (n = 22)	3 (13.6%)	18 (81.8%)	1 (4.5%)
60–69 (n = 15)	4 (26.7%)	10 (66.7%)	1 (6.7%)
≥70 (n = 6)	1 (16.7%)	3 (50.0%)	2 (33.3%)

6 DISCUSSION

The present study aimed to examine the generic HRQoL of unselected rhinologic patients with different rhinologic diseases, compare it to the HRQoL of patients with other chronic diseases from the same hospital district catchment area, and analyse any possible seasonality related to HRQoL. In addition, we aimed to determine whether the symptoms or HRQoL of rhinologic patients differed between work and leisure time, and whether specific occupational exposures explained this possible difference. The median sick leave of rhinologic patients was also analysed. Finally, we aimed to determine whether the original paper version of the generic HRQoL measurement tool, 15D, could be converted to an electronic format without compromising its reliability.

6.1 Comparison with Previous Studies

6.1.1 Generic HRQoL of rhinologic patients (study I)

Previous studies on the HRQoL of rhinologic patients have been performed primarily for specific diagnostic groups, such as CRS and AR patients (17, 131, 132, 136, 137, 230). But, studies on the HRQoL of unselected rhinologic patients do not appear in the literature, making comparisons with our study somewhat difficult. According to our study, patients with different rhinologic diseases have statistically significantly lower ($p < 0.001$) mean 15D scores than those amongst age- and sex-standardised general populations. Rhinologic patients fared more poorly on nearly all 15 dimensions of the questionnaire. In a previous study amongst CRS patients, the diminished HRQoL affected all domains of the generic 36-item short-form survey (SF-36) compared with healthy controls (231). HRQoL amongst AR patients also appears to decline widely (232). Some demographic factors, such as age, sex, and education, appear to affect the disease severity in CRS patients (9). Amongst CRS patients, women tend to experience greater HRQoL impairments than men and some domains are more affected amongst elderly and highly educated subjects (231). In our study, the 15D scores did not, however, differ significantly for women and men.

The HRQoL of our study patients was lower than that of many other patient groups (see Figure 4, page 40). Similar results for CRS patients were previously published, indicating that CRS patients fared more poorly than patients with many other diseases, such as (newly diagnosed) Parkinson's disease (17). One reason for the high burden of rhinologic diseases might result from a poor

quality of sleep and its impact on patients' everyday well-being. The possible high prevalence of comorbidities, such as asthma, OSA, and depression, may also play a role in the diminished HRQoL amongst our study patients.

Sleep quality in CRS and AR patients diminishes. Since a clear impact has been found for the disease severity of CRS on sleep quality (131), mucosal inflammation in these patients is thought to play a major role in sleep disturbance. The levels of several pro-inflammatory cytokines, such as TNF-α and IL-1β, appear to be elevated in CRS and AR patients, and these cytokines also associate with disrupted sleep (233-235). Nasal obstruction resulting from different inflammatory or noninflammatory causes serves as another independent factor associated with sleep dysfunction (130, 131, 236-239). In CRS patients, sleep and ear/facial domains more greatly associate with a diminished HRQoL (17, 240). Sleep is also heavily impaired in patients with AR, especially in patients with severe AR (241-243). Similarly, sleep was one of domains most affected amongst our study patients.

Comorbidities play a role in the diminished HRQoL of CRS and AR patients. For example, depression, fatigue, olfactory dysfunction, sleep disturbance, and sexual dysfunction associate with CRS and a reduced HRQoL (230). Specific illnesses such as asthma, OSA, depression, and COPD are more common amongst rhinologic patients, specifically CRS and AR, and associate with a diminished HRQoL (19, 20, 22, 133, 137, 244-246). One limitation to this study is the incomplete assessment of potentially relevant comorbidities. We systematically examined asthma amongst a proportion of patients, and an OSA diagnosis was based on sleep studies interpreted by physicians fragmented across different areas of the healthcare system. But, we did not specifically screen our patients for depression and COPD. In our study, the prevalence of asthma was 19.4%, which is higher, as anticipated, than the prevalence of asthma in the Finnish population (10%) (247). In the literature, the prevalence of asthma amongst CRS patients varies, ranging from 4% to 48%, with the highest prevelance occurring amongst CRSwNP patients (19, 248). AR patients are also at a high risk for developing asthma, with prevalence varying from 10% to 40% (242). Undiagnosed asthma is common amongst CRS patients. In a study conducted amongst patients with CRSwNP, 25% had undiagnosed asthma (249). Thus, a higher percentage of asthmatic patients should also be considered as possible in our study patients. The prevalence of OSA in Finland reaches 4.2%, but appears to be increasing (250, 251). Many rhinologic diseases serve as risk factors for the development of OSA. In two studies from the US, physician-diagnosed OSA was reported in 10.9% to 15% of CRS patients (252, 253). The frequency of OSA in our patients (10.5%) falls within that range. In a Taiwanese study, up to 64.7% CRS patients were diagnosed with OSA based on preoperative polysomnography screening (20). The discrepancy between these studies indicates that a potentially

significant proportion of CRS patients as well as our other study patients might have undiagnosed sleep apnoea.

There is still no consensus on what is considered a sufficient RR. In a recent systematic review article of RRs in the field of surgery, postal studies achieved an average RR of 68.0% ± 17.0% (254). Comparatively, our RR of 46% can be considered relatively low, although it is consistent with the average RR from a previous multicentre rhinologic study (8). It is important to keep in mind that we did not attempt to boost our RR.

6.1.2 Seasonal variation of HRQoL in rhinologic patients (study II)

Multiple studies have documented seasonal variation in the incidence, severity, and even mortality of many diseases (23, 24, 26-34, 36, 38, 39, 147). Few studies exist on the seasonality of HRQoL (42, 43, 255) such that a literature search identified only one study focusing on rhinologic patients specifically (43). In that study of disease-specific HRQoL amongst CRS patients, Talat et al. found that SNOT-22 score statistically but not clinically varied seasonally. According to their results, this seasonality was caused by the higher scores for the sleep and emotion subdomains during winter (43).

In respiratory diseases, particularly in a cold, humid environment, patients experience aggravated symptoms. In a Swedish study, most asthmatic patients reported cold as a factor causing breathing difficulties, whereby cold, damp air in particular caused more symptoms than cold, dry air (256). The upper airway mucosal structures are especially sensitive to cold air (257, 258). Cold air affects the nasal epithelium by activating nasal mast cells and causing sensory nerve stimulation, which results in nasal symptoms such as rhinorrhea and nasal congestion (259). Cold air not only cools but also dries the upper airways (260).

Finland lies approximately between the latitudes of 60º and 70º. Due to its location, Finland experiences four distinct seasons, with cold winters and warm summers. The indoor environment is directly influenced by the outdoor environment and, during winter, the population is exposed to cold air during their daily activities. In previous studies of the effects of cold air on the upper respiratory track, as well as our own clinical experience, we hypothesised that the symptoms and HRQoL of rhinologic patients worsen during the colder, drier winter season, and improve during the warmer, more humid summer season. In our study, however, this hypothesis was not supported given that the mean 15D, mean SNOT-22, and the mean values of the SNOT-22 subscales amongst rhinologic patients did not statistically vary by season. To our knowledge, this represents the first study in which the possible effect of seasonal weather variation associated with general and disease-specific HRQoL amongst groups of unselected rhinologic patients was investigated.

The mean temperatures during our study periods appeared somewhat different from normal climatic values. The largest differences were recorded for February (+0°C vs. −6°C), resulting in reduced exposure to cold thermal conditions compared to more typical winter conditions in Finland. This might have affected our results, since in a Finnish population–based study cold-related symptoms began emerging at relatively low temperatures (–14°C to –15°C) (261). In our study, the meteorological parameters observed included the mean temperature and mean absolute humidity. It is known that the effect of temperature is also modulated by other (often microclimatic) variables, such as air pressure and wind speed. However, according to a statement from the World Allergy Organisation, it might be difficult to obtain evidence of causality for specific respiratory diseases in such complex models (257). Furthermore, seasonal allergic rhinitis may decrease HRQoL during pollen season (262). But, since we had so few patients suffering from seasonal allergies in our data (n = 7, 2.3%), the impact of the pollen season is likely to remain small. The HUS catchment area, from whence we recruited study patients, is primarily urban. In total, 83% of our study patients lived in the three largest cities of Helsinki, Espoo, and Vantaa (data not shown). Additionally, the remaining patients primarily live in (smaller) cities. Thus, we extrapolate that only less than 10% live in the countryside. This small number of rural inhabitants does not allow for a comparison between the rural and the urban populations, which might have proved interesting.

SNOT-22 is validated only for CRS, although vast clinical and research experience exists on its usefulness for other rhinologic diseases or conditions as well (107, 138, 198, 263, 264). It was thus selected as the disease-specific HRQoL for our study. Notably, during the study period, the Finnish version of SNOT-22 was not yet validated, such that the validated version was released in 2017 (187, 197).

6.1.3 HRQoL of rhinologic patients at work (study III)

Nonspecific health problems and symptom worsening in the workplace are common. In an European study, one-third of office workers reported complaints about indoor air quality (265). In a study from the Finnish Institute for Health and Welfare in 2010, 42% of Finnish men and 25% of Finnish women reported some harm due to dust in the workplace (266). In a Belgian workforce study, work-related nasal symptoms associated with a significantly lower HRQoL when compared with non-work-related rhinologic symptoms (267). Individuals with nonspecific indoor air–related symptoms in general report a worse HRQoL than that amongst the general population (268). Our results are consistent albeit not directly comparable with these earlier studies since most of the rhinologic patients (60.1%) in our study reported worsening symptoms at work. Patients

who report worsening symptoms at work have a statistically significantly lower HRQoL based on their SNOT-22 scores when compared with those whose symptoms do not worsen at work. However, these differences were not found in the mean 15D scores. Female gender was previously related to more prevalent air-related symptoms (269, 270); but, in the current study, we did not observe this finding. In a query amongst Finnish workers, dry air, stale air, and dust were the most common complaints related to the indoor environment (271), which mirrors our findings.

Given that occupational exposures have been associated with airway symptoms (152), surprisingly in our study we found that specific occupational exposures did not appear to associate with aggravating symptoms or impact our study patients' HRQoL. Several factors may explain this. In Finland, if a patient is suspected of suffering from an occupational or work-related disease, they are referred directly to the Finnish Institute of Occupational Health. As a result, patients with the most troublesome symptoms at work are not generally treated in our clinic. Furthermore, based on our research, it seems that the patient referral process works well. The socioeconomic status of our study patients also differed from the general population, since our study population included more upper level and fewer manual labourers. This is also likely to have implications for our results given that specific occupational exposures are most common amongst manual labourers who may be subject to greater health risks on the job (48, 55, 152, 272, 273). Finally, the coverage of occupational health services reaches about 90% of all Finnish employees and Finland is known to have good occupational hygiene practices, likely reducing the risks for occupational exposures and diseases (274).

In the present study, rhinologic diseases only caused up to 7.7 days of work absences. Sickness absences amongst our study patients seem rather long compared with the all-cause sickness absences in Finland on average, which reached 9.1 days in 2020 (13). Socioeconomic differences in sickness absences have been well-documented: those in a lower occupational class report more sickness absences than those amongst a higher occupational class (275-278). Given that the socioeconomic status of our study patients was higher than the Finnish average, the burden caused by rhinologic diseases only in terms of increasing absenteeism may be even larger than assumed at present. Studies on sick leave amongst rhinologic patients appear in the literature for only a few diagnostic groups. CRS and AR have caused an average of 8–14 (14) and 0.6–9.9 (15, 16), respectively, work-days lost per year. Work-related rhinitis, on the other hand, has not been reported to associate with higher absenteeism rates (267).

6.1.4 15D: From pen-and-paper to an electronic format (study IV)

Based on study IV, we found that the 15D questionnaire can be converted to an electronic format without markedly affecting data equivalence. When comparing the paper- and electronic-based 15D scores, we found a moderate-to-high correlation. In a systematic Cochrane database review, Marcano Belisario et al. reported similar results regarding data equivalence when comparing the application-based queries to other delivery modes.(73) Furthermore, they found no significant differences in the mean scores between different data collection methods and all ICCs exceeded the recommended thresholds (73). Two other meta-analyses reported similar results (66, 74).

In the present study, amongst study group two, in which patients first completed a paper and then an application–based form, the 95% CI of the ICC estimate did not exceed the recommended 0.7. When analysing the possible causative factors for this, several explanations emerged. The sample size in this study group was below the recommended minimum and was also smaller than that in other groups, possibly highlighting potential errors. The HRQoL of patients in this study group was lower (data not shown) than that in other study groups, and a greater potential for an HRQoL improvement may have resulted from the statistically and clinically significant improvement in the second measurement. Remarkably, the degree of changes from the paper format also varied between the application and web-based formats. Based on ISPOR's recommendations, the changes were moderate in the former group, but only minor in the latter (5). However, in the other study group which also completed the application-based format, study group 4, the repeated measures results were consistent, thereby reducing the likelihood that the interpretability of the application form was impaired.

A majority of patients (74.1%) preferred electronic modalities over the paper-based format. Similarly, previous studies have shown that patients prefer electronic formats, although this is influenced by multiple demographic factors (4, 78-83). In the present study, patients preferred the electronic modalities across all age groups and regardless of gender, although the difference between gender and format preference was indicative but not statistically significant (data not shown).

An electronic format resulted in lower RRs than paper formats in our study, at least if completed at home. A recent review article also found the highest RR for paper formats (86% ± 19.4%), with the second highest RR found for a mixture of electronic and paper formats (71% ± 15.1%), whilst the electronic format had the lowest RR (42% ± 8.7%) (86). This finding is supported by various previous studies (4, 81, 84, 85) and also by a recent meta-analysis showing a 12% RR difference between web-based surveys and other modes (279). By contrast, Rutherford et al. completed a systematic review of optimal modes of patient-

reported outcome measurement (PROM) administration, finding no systematic difference in RRs (74). There are, however, several methods to improving RRs, such as reminder messages (86, 88), which we did not perform in our study. In addition to possibly lower RRs, a few other risks have been associated with electronic PROM formats. In a longitudinal study of diabetes patients, the sociodemographic and health profile of patients differed significantly across different data collection methods. Researchers assumed this resulted from different recruitment methods and differences in those choosing to respond to different survey versions (80). Without offering a paper format option, important subgroups, such as individuals with less education, women, fully retired individuals, and unmarried individuals, might be underrepresented or missing from studies (280, 281). Since survey RRs have also continued declining for many years, data collection methods should be selected carefully to ensure as representative and as large a population as possible is collected (282).

6.2 Future Research

This thesis and its results offer not only clinical implications but also new perspectives for future research. Study I emphasises that signs of comorbidities such as asthma and OSA should be screened in future studies in order to assess the possibility and magnitude of their impact particularly on the quality of sleep amongst rhinologic patients, which should also be an important aim in clinical practice. The findings from study I may impact the allocation of treatment and research in rhinologic clinics.

The results from study II establish the use of 15D and SNOT-22 as tools in clinical practice and research, since considering the role of seasons might not be necessary. The interyear variability of climatic factors remains moderately large and further studies are needed in order to confirm our findings. Since our study is cross-sectional, patient-level studies should also be performed in future.

Although the primary triggers at work remained nonspecific in study III, the possibility of specific occupational diseases should be taken into consideration during each patient evaluation. Our study sample primarily consisted of upper level empolyees and further studies focusing on manual labourers are needed. Rhinologic diseases associate with substantial work productivity loss due to absenteeism, highlighting the importance of disease management.

Finally, study IV provides valuable information for further studies amongst other patient groups and in larger patient cohorts. Based on our research, we recommend the use of 15D electronic data collection methods. However, given issues related to the equality of patients and diversity across demographic characteristics across patients in research settings, we recommend providing paper-based formats alongside electronic formats.

7 CONCLUSIONS

Study I demonstrates that rhinologic diseases cause a multidimensional decrease in patients' generic HRQoL, an impairment independent of the specific diagnosis. Rhinologic diseases appear to impact, amongst others, patients' sleep, breathing, and vitality. Furthermore, comorbidities such as asthma and OSA are common amongst rhinologic patients.

Study II, conducted in a country with four distinct seasons, demonstrates that no statistically significant seasonality exists in the generic or disease-specific HRQoL amongst our study patients with different rhinologic diseases or symptoms.

Findings from study III provided an important understanding of the work-related symptoms across the entire spectrum of rhinologic diseases and their relationship to specific occupational exposures. According to our results, exposure to specific occupational exposures or irritants is not associated with aggravating symptoms or a diminished HRQoL at work amongst patients with different rhinologic diseases. Most rhinologic patients experienced exacerbated symptoms at work, however.

Based on findings from study IV, the electronic version of the generic HRQoL measurement tool, 15D, is quantitatively comparable with measurements relying on the original paper version.

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REFERENCES

1. Pequeno NPF, Cabral NLdA, Marchioni DM, Lima SCVC, Lyra CdO. Quality of life assessment instruments for adults: a systematic review of population-based studies. Health and quality of life outcomes. 2020;18(1):208.
2. Patrick DL, Deyo RA. Generic and disease-specific measures in assessing health status and quality of life. Med Care. 1989;27(3 Suppl):S217-32.
3. Malý M, Vondra V. Generic versus disease-specific instruments in quality-of-life assessment of chronic obstructive pulmonary disease. Methods Inf Med. 2006;45(2):211-5.
4. Meirte J, Hellemans N, Anthonissen M, Denteneer L, Maertens K, Moortgat P, et al. Benefits and Disadvantages of Electronic Patient-reported Outcome Measures: Systematic Review. JMIR Perioper Med. 2020;3(1):e15588-e.
5. Coons SJ, Gwaltney CJ, Hays RD, Lundy JJ, Sloan JA, Revicki DA, et al. Recommendations on Evidence Needed to Support Measurement Equivalence between Electronic and Paper-Based Patient-Reported Outcome (PRO) Measures: ISPOR ePRO Good Research Practices Task Force Report. Value in Health. 2009;12(4):419-29.
6. Bauchau V, Durham SR. Prevalence and rate of diagnosis of allergic rhinitis in Europe. Eur Respir J. 2004;24(5):758-64.
7. Haahtela T, von Hertzen L, Makela M, Hannuksela M, Grp APW. Finnish Allergy Programme 2008-2018 - time to act and change the course. Allergy. 2008;63(6):634-45.
8. Hastan D, Fokkens WJ, Bachert C, Newson RB, Bislimovska J, Bockelbrink A, et al. Chronic rhinosinusitis in Europe--an underestimated disease. A GA(2)LEN study. Allergy. 2011;66(9):1216-23.
9. Fokkens WJ, Lund VJ, Hopkins C, Hellings PW, Kern R, Reitsma S, et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2020. Rhinology. 2020;58(Suppl S29):1-464.
10. Hoffmans R, Wagemakers A, van Drunen C, Hellings P, Fokkens W. Acute and chronic rhinosinusitis and allergic rhinitis in relation to comorbidity, ethnicity and environment. PLoS One. 2018;13(2):e0192330.
11. Caulley L, Thavorn K, Rudmik L, Cameron C, Kilty SJ. Direct costs of adult chronic rhinosinusitis by using 4 methods of estimation: Results of the US Medical Expenditure Panel Survey. J Allergy Clin Immunol. 2015;136(6):1517-22.
12. Nurmagambetov T, Kuwahara R, Garbe P. The Economic Burden of Asthma in the United States, 2008-2013. Ann Am Thorac Soc. 2018;15(3):348-56.
13. Kela. Kelan tilastollinen vuosikirja 2020. Kela; 2021.

14. Sahlstrand-Johnson P, Ohlsson B, Von Buchwald C, Jannert M, Ahlner-Elmqvist M. A multi-centre study on quality of life and absenteeism in patients with CRS referred for endoscopic surgery. Rhinology. 2011;49(4):420-8.

15. Bhattacharyya N. Functional limitations and workdays lost associated with chronic rhinosinusitis and allergic rhinitis. American journal of rhinology & allergy. 2012;26(2):120-2.

16. Vandenplas O, Vinnikov D, Blanc PD, Agache I, Bachert C, Bewick M, et al. Impact of Rhinitis on Work Productivity: A Systematic Review. The journal of allergy and clinical immunology In practice. 2018;6(4):1274-86.e9.

17. DeConde AS, Soler ZM. Chronic rhinosinusitis: Epidemiology and burden of disease. American journal of rhinology & allergy. 2016;30(2):134-9.

18. Bousquet J, Van Cauwenberge P, Khaltaev N, Aria Workshop G, World Health O. Allergic rhinitis and its impact on asthma. J Allergy Clin Immunol. 2001;108(5 Suppl):S147-334.

19. Promsopa C, Kansara S, Citardi MJ, Fakhri S, Porter P, Luong A. Prevalence of confirmed asthma varies in chronic rhinosinusitis subtypes. Int Forum Allergy Rhinol. 2016;6(4):373-7.

20. Jiang RS, Liang KL, Hsin CH, Su MC. The impact of chronic rhinosinusitis on sleep-disordered breathing. Rhinology. 2016;54(1):75-9.

21. Schlosser RJ, Gage SE, Kohli P, Soler ZM. Burden of illness: A systematic review of depression in chronic rhinosinusitis. American journal of rhinology & allergy. 2016;30(4):250-6.

22. Smith KA, Alt JA. The relationship of chronic rhinosinusitis and depression. Curr Opin Otolaryngol Head Neck Surg. 2020;28(1):1-5.

23. Tedijanto C, Hermans S, Cobelens F, Wood R, Andrews JR. Drivers of Seasonal Variation in Tuberculosis Incidence: Insights from a Systematic Review and Mathematical Model. Epidemiology. 2018;29(6):857-66.

24. Yu J, Yang D, Kim Y, Hashizume M, Gasparrini A, Armstrong B, et al. Seasonality of suicide: a multi-country multi-community observational study. Epidemiol Psychiatr Sci. 2020;29:e163.

25. Ilves I, Fagerstrom A, Herzig KH, Juvonen P, Miettinen P, Paajanen H. Seasonal variations of acute appendicitis and nonspecific abdominal pain in Finland. World J Gastroenterol. 2014;20(14):4037-42.

26. York TJ. Seasonal and climatic variation in the incidence of adult acute appendicitis: a seven year longitudinal analysis. BMC Emerg Med. 2020;20(1):24.

27. Liguori C, Holzknecht E, Placidi F, Izzi F, Mercuri NB, Högl B, et al. Seasonality of restless legs syndrome: symptom variability in winter and summer times. Sleep Med. 2020;66:10-4.

28. Greenfeld M, Sivan Y, Tauman R. The effect of seasonality on sleep-disordered breathing severity in children. Sleep Medicine. 2013;14(10):991-4.

29. Geoffroy PA, Bellivier F, Scott J, Etain B. Seasonality and bipolar disorder: a systematic review, from admission rates to seasonality of symptoms. J Affect Disord. 2014;168:210-23.

30. Moineddin R, Nie JX, Domb G, Leong AM, Upshur REG. Seasonality of primary care utilization for respiratory diseases in Ontario: A time-series analysis. BMC Health Services Research. 2008;8(1):160.

31. Shrestha P, Poudel DR, Dhital R, Karmacharya P. Seasonal and regional variation of asthma-related hospitalizations and mortality among adults in the United States. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology. 2018;121(3):368-9.

32. Canova C, Heinrich J, Anto JM, Leynaert B, Smith M, Kuenzli N, et al. The influence of sensitisation to pollens and moulds on seasonal variations in asthma attacks. European Respiratory Journal. 2013;42(4):935.

33. Witonsky J, Abraham R, Toh J, Desai T, Shum M, Rosenstreich D, et al. The association of environmental, meteorological, and pollen count variables with asthma-related emergency department visits and hospitalizations in the Bronx. The Journal of asthma : official journal of the Association for the Care of Asthma. 2019;56(9):927-37.

34. Callaly E, Mikulich O, Silke B. Increased winter mortality: the effect of season, temperature and deprivation in the acutely ill medical patient. Eur J Intern Med. 2013;24(6):546-51.

35. Rolden HJ, Rohling JH, van Bodegom D, Westendorp RG. Seasonal Variation in Mortality, Medical Care Expenditure and Institutionalization in Older People: Evidence from a Dutch Cohort of Older Health Insurance Clients. PLoS One. 2015;10(11):e0143154.

36. Ryti NR, Guo Y, Jaakkola JJ. Global Association of Cold Spells and Adverse Health Effects: A Systematic Review and Meta-Analysis. Environmental health perspectives. 2016;124(1):12-22.

37. Yu Y, Luo S, Zhang Y, Liu L, Wang K, Hong L, et al. Comparative analysis of daily and hourly temperature variability in association with all-cause and cardiorespiratory mortality in 45 US cities. Environ Sci Pollut Res Int. 2022;29(8):11625-33.

38. Purkey MR, Seeskin Z, Chandra R. Seasonal variation and predictors of epistaxis. Laryngoscope. 2014;124(9):2028-33.

39. Rank MA, Wollan P, Kita H, Yawn BP. Acute exacerbations of chronic rhinosinusitis occur in a distinct seasonal pattern. The Journal of allergy and clinical immunology. 2010;126(1):168-9.

40. Kuiper JR, Hirsch AG, Bandeen-Roche K, Sundaresan AS, Tan BK, Schleimer RP, et al. Prevalence, severity, and risk factors for acute exacerbations of nasal and sinus symptoms by chronic rhinosinusitis status. Allergy. 2018;73(6):1244-53.

41. Jia H, Lubetkin EI. Time Trends and Seasonal Patterns of Health-Related Quality of Life Among U.S. Adults. Public health reports. 2009;124(5):692-701.

42. Grimaldi S, Partonen T, Saarni SI, Aromaa A, Lonnqvist J. Indoors illumination and seasonal changes in mood and behavior are associated with the health-related quality of life. Health and quality of life outcomes. 2008;6:56.

43. Talat R, Phillips KM, Caradonna DS, Gray ST, Sedaghat AR. Seasonal variations in chronic rhinosinusitis symptom burden may be explained by changes in mood. Eur Arch Otorhinolaryngol. 2019;276(10):2803-9.

44. Castano R, Thériault G. Defining and classifying occupational rhinitis. J Laryngol Otol. 2006;120(10):812-7.

45. Tarlo SM. Update on work-exacerbated asthma. Int J Occup Med Environ Health. 2016;29(3):369-74.

46. Tiotiu AI, Novakova S, Labor M, Emelyanov A, Mihaicuta S, Novakova P, et al. Progress in Occupational Asthma. Int J Environ Res Public Health. 2020;17(12):4553.

47. Tarlo SM, Lemiere C. Occupational asthma. N Engl J Med. 2014;370(7):640-9.

48. Miedinger D, Malo JL, Ghezzo H, L'Archevêque J, Zunzunegui MV. Factors influencing duration of exposure with symptoms and costs of occupational asthma. Eur Respir J. 2010;36(4):728-34.

49. Vandenplas O, Malo JL. Definitions and types of work-related asthma: a nosological approach. Eur Respir J. 2003;21(4):706-12.

50. Siracusa A, Desrosiers M, Marabini A. Epidemiology of occupational rhinitis: prevalence, aetiology and determinants. Clin Exp Allergy. 2000;30(11):1519-34.

51. Hytönen M, Kanerva L, Malmberg H, Martikainen R, Mutanen P, Toikkanen J. The risk of occupational rhinitis. Int Arch Occup Environ Health. 1997;69(6):487-90.

52. Olivieri M, Malerba M, Spiteri G, Torroni L, Biscardo CA, Valenza D, et al. Fractional exhaled nitric oxide levels in relation to work-related respiratory burden and sensitization to wheat flour and multigrain in bakers. Clin Transl Allergy. 2021;11(8):e12018.

53. Moscato G, Vandenplas O, Gerth Van Wijk R, Malo JL, Quirce S, Walusiak J, et al. Occupational rhinitis. Allergy. 2008;63(8):969-80.

54. Sublett JW, Bernstein DI. Occupational Rhinitis. Current Allergy and Asthma Reports. 2010;10(2):99-104.

55. Thilsing T, Rasmussen J, Lange B, Kjeldsen AD, Al-Kalemji A, Baelum J. Chronic rhinosinusitis and occupational risk factors among 20- to 75-year-old Danes-A GA(2) LEN-based study. American journal of industrial medicine. 2012;55(11):1037-43.

56. Koh DH, Kim HR, Han SS. The relationship between chronic rhinosinusitis and occupation: the 1998, 2001, and 2005 Korea National health and nutrition examination survey (KNHANES). American journal of industrial medicine. 2009;52(3):179-84.

57. Clarhed UKE, Johansson H, Veel Svendsen M, Toren K, Moller AK, Hellgren J. Occupational exposure and the risk of new-onset chronic rhinosinusitis â€" a prospective study 2013-2018. Rhinology. 2020;58(6):597-604.

58. Gao WX, Ou CQ, Fang SB, Sun YQ, Zhang H, Cheng L, et al. Occupational and environmental risk factors for chronic rhinosinusitis in China: a multicentre cross-sectional study. Respiratory research. 2016;17(1):54.

59. FDA. Guidance for Industry. Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims: Food and Drug Administration U.S. Department of Health and Human Services; 2009 [Available from: https://www.fda.gov/media/77832/download.

60. Markets Ra. Global EPRO, ePatient Diaries, and eCOA Market Size, Trends & Growth, Opportunity, By Type, By End User, By Region and Forecast till 2027 2021 [Available from: https://www.researchandmarkets.com/reports/5398510/global-epro-epatient-diaries-and-ecoa-market.

61. Rothman M, Burke L, Erickson P, Leidy NK, Patrick DL, Petrie CD. Use of existing patient-reported outcome (PRO) instruments and their modification: the ISPOR Good Research Practices for Evaluating and Documenting Content Validity for the Use of Existing Instruments and Their Modification PRO Task Force Report. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2009;12(8):1075-83.

62. Muehlhausen W, Doll H, Quadri N, Fordham B, O'Donohoe P, Dogar N, et al. Equivalence of electronic and paper administration of patient-reported outcome measures: a systematic review and meta-analysis of studies conducted between 2007 and 2013. Health and quality of life outcomes. 2015;13:167.

63. Willis GB RB, Barofsky I. The use of cognitive interviewing techniques in quality of life and patient-reported outcomes assessment.: Cambridge University Press; 2005.

64. Aiyegbusi OL. Key methodological considerations for usability testing of electronic patient-reported outcome (ePRO) systems. Qual Life Res. 2020;29(2):325-33.

65. Frost MH, Reeve BB, Liepa AM, Stauffer JW, Hays RD. What is sufficient evidence for the reliability and validity of patient-reported outcome measures? Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2007;10 Suppl 2:S94-s105.

66. Gwaltney CJ, Shields AL, Shiffman S. Equivalence of electronic and paper-and-pencil administration of patient-reported outcome measures: a meta-analytic review. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2008;11(2):322-33.

67. Shields A, Gwaltney C, Tiplady B, Paty J, Shiffman S. Grasping the FDA's PRO Guidance. Clinical Trials. 2006;15:69-72.

68. Quadri N, Wild D, Skerritt B, Muehlhausen W, O'Donohoe P. PRM153. A literature review of the variance in interval length between administrations for assessment of test retest reliability and equivalence of pro measures. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2013;16:A40-1.

69. Koo TK, Li MY. A Guideline of Selecting and Reporting Intraclass Correlation Coefficients for Reliability Research. J Chiropr Med. 2016;15(2):155-63.

70. Byrom B, Doll H, Muehlhausen W, Flood E, Cassedy C, McDowell B, et al. Measurement Equivalence of Patient-Reported Outcome Measure Response Scale Types Collected Using Bring Your Own Device Compared to Paper and a Provisioned Device: Results of a Randomized Equivalence Trial. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2018;21(5):581-9.

71. Byrom B, Elash CA, Eremenco S, Bodart S, Muehlhausen W, Platko JV, et al. Measurement Comparability of Electronic and Paper Administration of Visual Analogue Scales: A Review of Published Studies. Therapeutic Innovation & Regulatory Science. 2022;56(3):394-404.

72. White MK, Maher SM, Rizio AA, Bjorner JB. A meta-analytic review of measurement equivalence study findings of the SF-36(R) and SF-12(R) Health Surveys across electronic modes compared to paper administration. Qual Life Res. 2018;27(7):1757-67.

73. Marcano Belisario JS, Jamsek J, Huckvale K, O'Donoghue J, Morrison CP, Car J. Comparison of self-administered survey questionnaire responses collected using mobile apps versus other methods. Cochrane Database Syst Rev. 2015;2015(7):Mr000042.

74. Rutherford C, Costa D, Mercieca-Bebber R, Rice H, Gabb L, King M. Mode of administration does not cause bias in patient-reported outcome results: a meta-analysis. Qual Life Res. 2016;25(3):559-74.

75. Jibb LA, Khan JS, Seth P, Lalloo C, Mulrooney L, Nicholson K, et al. Electronic Data Capture Versus Conventional Data Collection Methods in Clinical Pain Studies: Systematic Review and Meta-Analysis. J Med Internet Res. 2020;22(6):e16480.

76. Bennett AV, Dueck AC, Mitchell SA, Mendoza TR, Reeve BB, Atkinson TM, et al. Mode equivalence and acceptability of tablet computer-, interactive voice response system-, and paper-based administration of the U.S. National Cancer Institute's Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). Health and quality of life outcomes. 2016;14:24.

77. Bjorner JB, Rose M, Gandek B, Stone AA, Junghaenel DU, Ware JE, Jr. Method of administration of PROMIS scales did not significantly impact score level, reliability, or validity. J Clin Epidemiol. 2014;67(1):108-13.

78. Pathiravasan CH, Zhang Y, Trinquart L, Benjamin EJ, Borrelli B, McManus DD, et al. Adherence of Mobile App-Based Surveys and Comparison With Traditional Surveys: eCohort Study. J Med Internet Res. 2021;23(1):e24773.

79. Gamper EM, Nerich V, Sztankay M, Martini C, Giesinger JM, Scarpa L, et al. Evaluation of Noncompletion Bias and Long-Term Adherence in a 10-Year Patient-Reported Outcome Monitoring Program in Clinical Routine. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2017;20(4):610-7.

80. Rowen D, Carlton J, Elliott J. PROM Validation Using Paper-Based or Online Surveys: Data Collection Methods Affect the Sociodemographic and Health Profile of the Sample. Value in Health. 2019;22(8):845-50.

81. Blumenberg C, Barros AJD. Response rate differences between web and alternative data collection methods for public health research: a systematic review of the literature. Int J Public Health. 2018;63(6):765-73.

82. Graf J, Simoes E, Wißlicen K, Rava L, Walter CB, Hartkopf A, et al. Willingness of Patients with Breast Cancer in the Adjuvant and Metastatic Setting to Use Electronic Surveys (ePRO) Depends on Sociodemographic Factors, Health-related Quality of Life, Disease Status and Computer Skills. Geburtshilfe Frauenheilkd. 2016;76(5):535-41.

83. Drummond HE, Ghosh S, Ferguson A, Brackenridge D, Tiplady B. Electronic quality of life questionnaires: a comparison of pen-based electronic questionnaires with conventional paper in a gastrointestinal study. Qual Life Res. 1995;4(1):21-6.

84. Palmen LN, Schrier JC, Scholten R, Jansen JH, Koëter S. Is it too early to move to full electronic PROM data collection?: A randomized controlled trial comparing PROM's after hallux valgus captured by e-mail, traditional mail and telephone. Foot Ankle Surg. 2016;22(1):46-9.

85. Rolfson O, Salomonsson R, Dahlberg LE, Garellick G. Internet-based follow-up questionnaire for measuring patient-reported outcome after total hip replacement surgery-reliability and response rate. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2011;14(2):316-21.

86. Wang K, Eftang CN, Jakobsen RB, Årøen A. Review of response rates over time in registry-based studies using patient-reported outcome measures. BMJ Open. 2020;10(8):e030808.

87. Wintner LM, Sztankay M, Riedl D, Rumpold G, Nickels A, Licht T, et al. How to implement routine electronic patient-reported outcome monitoring in oncology rehabilitation. International Journal of Clinical Practice. 2021;75(4):e13694.

88. Edwards PJ, Roberts I, Clarke MJ, Diguiseppi C, Wentz R, Kwan I, et al. Methods to increase response to postal and electronic questionnaires. Cochrane Database Syst Rev. 2009;2009(3):Mr000008.

89. The World Health Organization Quality of Life assessment (WHOQOL): position paper from the World Health Organization. Soc Sci Med. 1995;41(10):1403-9.

90. Karimi M, Brazier J. Health, Health-Related Quality of Life, and Quality of Life: What is the Difference? Pharmacoeconomics. 2016;34(7):645-9.

91. Bowling A. What things are important in people's lives? A survey of the public's judgements to inform scales of health related quality of life. Soc Sci Med. 1995;41(10):1447-62.

92. Spitzer WO, Dobson AJ, Hall J, Chesterman E, Levi J, Shepherd R, et al. Measuring the quality of life of cancer patients: a concise QL-index for use by physicians. J Chronic Dis. 1981;34(12):585-97.

93. Ware JE, Jr. Standards for validating health measures: definition and content. J Chronic Dis. 1987;40(6):473-80.

94. Guyatt GH, Feeny DH, Patrick DL. Measuring health-related quality of life. Ann Intern Med. 1993;118(8):622-9.

95. Guyatt GH, Veldhuyzen Van Zanten SJ, Feeny DH, Patrick DL. Measuring quality of life in clinical trials: a taxonomy and review. Cmaj. 1989;140(12):1441-8.

96. Coons SJ, Rao S, Keininger DL, Hays RD. A comparative review of generic quality-of-life instruments. Pharmacoeconomics. 2000;17(1):13-35.

97. Hyland ME. A brief guide to the selection of quality of life instrument. Health and quality of life outcomes. 2003;1(1):24.

98. Higginson IJ, Carr AJ. Measuring quality of life: Using quality of life measures in the clinical setting. Bmj. 2001;322(7297):1297-300.

99. Hays R, Reeve BB. Measurement and Modeling of Health-Related Quality of Life. International Encyclopedia of Public Health. 2008:241-52.

100. Institute of Medicine Council on Health Care T. In: Mosteller F, Falotico-Taylor J, editors. Quality of Life and Technology Assessment: Monograph of the Council on Health Care Technology. Washington (DC): National Academies Press (US) Copyright © National Academy of Sciences.; 1989.

101. Weinstein MC, Torrance G, McGuire A. QALYs: the basics. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2009;12 Suppl 1:S5-9.

102. Sassi F. Calculating QALYs, comparing QALY and DALY calculations. Health Policy and Planning. 2006;21(5):402-8.

103. Sintonen H. The 15D instrument of health-related quality of life: properties and applications. Ann Med. 2001;33(5):328-36.

104. Devlin N, Parkin D, Janssen B. Methods for Analysing and Reporting EQ-5D Data. Cham (CH): Springer Copyright 2020, The Editor(s) (if applicable) and The Author(s). This book is an open access publication.; 2020.

105. Horsman J, Furlong W, Feeny D, Torrance G. The Health Utilities Index (HUI): concepts, measurement properties and applications. Health and quality of life outcomes. 2003;1:54.

106. Hytonen ML, Lilja M, Makitie AA, Sintonen H, Roine RP. Does septoplasty enhance the quality of life in patients? EurArchOtorhinolaryngol. 2012;269(12):2497-503.

107. Alakarppa AI, Koskenkorva TJ, Koivunen PT, Alho OP. Quality of life before and after sinonasal surgery: a population-based matched cohort study. European Archives of Oto-Rhino-Laryngology. 2017;274(2):795-802.

108. Scadding G, Hellings P, Alobid I, Bachert C, Fokkens W, van Wijk RG, et al. Diagnostic tools in Rhinology EAACI position paper. Clinical and Translational Allergy. 2011;1(1):2.

109. Petersen KD, Kronborg C, Gyrd-Hansen D, Dahl R, Larsen JN, Løwenstein H. Quality of life in rhinoconjunctivitis assessed with generic and disease-specific questionnaires. Allergy. 2008;63(3):284-91.

110. Makatsori M, Koulias C, Calderon MA. Health-Related Quality of Life and Rhinitis Control Measures in Allergic Rhinitis. Current Treatment Options in Allergy. 2014;1(1):27-38.

111. Hendry J, Chin A, Swan IR, Akeroyd MA, Browning GG. The Glasgow Benefit Inventory: a systematic review of the use and value of an otorhinolaryngological generic patient-recorded outcome measure. Clin Otolaryngol. 2016;41(3):259-75.

112. Hopkins C. Patient reported outcome measures in rhinology. Rhinology. 2009;47(1):10-7.

113. Wisløff T, Hagen G, Hamidi V, Movik E, Klemp M, Olsen JA. Estimating QALY gains in applied studies: a review of cost-utility analyses published in 2010. Pharmacoeconomics. 2014;32(4):367-75.

114. Hopkins C, Gillett S, Slack R, Lund VJ, Browne JP. Psychometric validity of the 22-item Sinonasal Outcome Test. Clin Otolaryngol. 2009;34(5):447-54.

115. Sartorio A, Agosti F, De Col A, Castelnuovo G, Manzoni GM, Molinari E, et al. Concurrent comparison of the measurement properties of generic and disease-specific questionnaires in obese inpatients. J Endocrinol Invest. 2014;37(1):31-42.

116. Mazur W, Kupiainen H, Pitkäniemi J, Kilpeläinen M, Sintonen H, Lindqvist A, et al. Comparison between the disease-specific Airways Questionnaire 20 and the generic 15D instruments in COPD. Health and quality of life outcomes. 2011;9:4.

117. Touma Z, Gladman DD, Ibañez D, Urowitz MB. Is there an advantage over SF-36 with a quality of life measure that is specific to systemic lupus erythematosus? J Rheumatol. 2011;38(9):1898-905.

118. Marra CA, Woolcott JC, Kopec JA, Shojania K, Offer R, Brazier JE, et al. A comparison of generic, indirect utility measures (the HUI2, HUI3, SF-6D, and the EQ-5D) and disease-specific instruments (the RAQoL and the HAQ) in rheumatoid arthritis. Soc Sci Med. 2005;60(7):1571-82.

119. Puhan MA, Gaspoz JM, Bridevaux PO, Schindler C, Ackermann-Liebrich U, Rochat T, et al. Comparing a disease-specific and a generic health-related quality of life instrument in subjects with asthma from the general population. Health and quality of life outcomes. 2008;6:15.

120. Seow LSE, Tan THG, Abdin E, Chong SA, Subramaniam M. Comparing disease-specific and generic quality of life measures in patients with schizophrenia. Psychiatry Res. 2019;273:387-93.

121. Tu XJ, Hwang WJ, Ma HI, Chang LH, Hsu SP. Determinants of generic and specific health-related quality of life in patients with Parkinson's disease. PLoS One. 2017;12(6):e0178896.

122. Lappalainen L, Stenvall H, Lavikainen P, Miettinen H, Martikainen J, Sintonen H, et al. Patient-reported outcomes in coronary artery disease: the relationship between the standard, disease-specific set by the International Consortium for Health Outcomes Measurement (ICHOM) and the generic health-related quality of life instrument 15D. Health and quality of life outcomes. 2021;19(1):206.

123. Ozdoganoglu T, Songu M, Inancli HM. Quality of life in allergic rhinitis. Ther Adv Respir Dis. 2012;6(1):25-39.

124. Haahtela T, von Hertzen L, Mäkelä M, Hannuksela M. Finnish Allergy Programme 2008-2018--time to act and change the course. Allergy. 2008;63(6):634-45.

125. OECD, Union E. Health at a Glance: Europe 20202020.

126. Selroos O, Kupczyk M, Kuna P, Łacwik P, Bousquet J, Brennan D, et al. National and regional asthma programmes in Europe. Eur Respir Rev. 2015;24(137):474-83.

127. Rudmik L, Smith TL, Schlosser RJ, Hwang PH, Mace JC, Soler ZM. Productivity costs in patients with refractory chronic rhinosinusitis. Laryngoscope. 2014;124(9):2007-12.

128. Smith KA, Orlandi RR, Rudmik L. Cost of adult chronic rhinosinusitis: A systematic review. Laryngoscope. 2015;125(7):1547-56.

129. Economic Costs of Diabetes in the U.S. in 2017. Diabetes Care. 2018;41(5):917-28.

130. Fried J, Yuen E, Li A, Zhang K, Nguyen SA, Gudis DA, et al. Rhinologic disease and its impact on sleep: a systematic review. Int Forum Allergy Rhinol. 2021;11(7):1074-86.

131. Bengtsson C, Lindberg E, Jonsson L, Holmström M, Sundbom F, Hedner J, et al. Chronic Rhinosinusitis Impairs Sleep Quality: Results of the GA2LEN Study. Sleep. 2017;40(1).

132. Klonaris D, Doulaptsi M, Karatzanis A, Velegrakis S, Milioni A, Prokopakis E. Assessing quality of life and burden of disease in chronic rhinosinusitis: a review. Rhinology Online. 2019;2:6-13.

133. Schlosser RJ, Gage SE, Kohli P, Soler ZM. Burden of illness: A systematic review of depression in chronic rhinosinusitis. American journal of rhinology & allergy. 2016;30(4):250-6.

134. Teul I, Zbisławski W, Baran S, Czerwiński F, Lorkowski J. Quality of life of patients with diseases of sinuses. J Physiol Pharmacol. 2007;58 Suppl 5(Pt 2):691-7.

135. Stjärne P, Odebäck P, Ställberg B, Lundberg J, Olsson P. High costs and burden of illness in acute rhinosinusitis: real-life treatment patterns and outcomes in Swedish primary care. Prim Care Respir J. 2012;21(2):174-9; quiz 10p following 9.

136. Bousquet J, Van Cauwenberge P, Khaltaev N. Allergic rhinitis and its impact on asthma. J Allergy Clin Immunol. 2001;108(5 Suppl):S147-334.

137. Al-Digheari A, Mahboub B, Tarraf H, Yucel T, Annesi-Maesano I, Doble A, et al. The clinical burden of allergic rhinitis in five Middle Eastern countries: results of the SNAPSHOT program. Allergy Asthma Clin Immunol. 2018;14:63.

138. Hytönen ML, Lilja M, Mäkitie AA, Sintonen H, Roine RP. Does septoplasty enhance the quality of life in patients? Eur Arch Otorhinolaryngol. 2012;269(12):2497-503.

139. Alakärppä AI, Koskenkorva TJ, Koivunen PT, Alho OP. Quality of life before and after sinonasal surgery: a population-based matched cohort study. Eur Arch Otorhinolaryngol. 2017;274(2):795-802.

140. Valsamidis K, Printza A, Titelis K, Constantinidis J, Triaridis S. Olfaction and quality of life in patients with nasal septal deviation treated with septoplasty. Am J Otolaryngol. 2019;40(5):747-54.

141. Balbus J, Berry P, Brettle M, Jagnarine-Azan S, Soares A, Ugarte C, et al. Enhancing the sustainability and climate resiliency of health care facilities: a comparison of initiatives and toolkits. Rev Panam Salud Publica. 2016;40(3):174-80.

142. Kalkstein LS, and Valimont, K. M. CLIMATE EFFECTS ON HUMAN HEALTH. Potential effects of future climate changes on forests and vegetation, agriculture, water resources, and human health. 1987(EPA Science and Advisory Committee Monograph no. 25389):122-52. .

143. Watts N, Amann M, Arnell N, Ayeb-Karlsson S, Beagley J, Belesova K, et al. The 2020 report of The Lancet Countdown on health and climate change: responding to converging crises. Lancet. 2021;397(10269):129-70.

144. Naclerio R, Ansotegui IJ, Bousquet J, Canonica GW, D'Amato G, Rosario N, et al. International expert consensus on the management of allergic rhinitis (AR) aggravated by air pollutants: Impact of air pollution on patients with AR: Current knowledge and future strategies. The World Allergy Organization journal. 2020;13(3):100106.

145. Zhang Y, Steiner AL. Projected climate-driven changes in pollen emission season length and magnitude over the continental United States. Nature Communications. 2022;13(1):1234.

146. Tuomenvirta. Weather and Climate Risks in Finland - National Assessment. . https://julkaisut.valtioneuvosto.fi/bitstream/handle/10024/161015/43-2018-Saa%20ja%20ilmastoriskit%20Suomessa.pdf?sequence=1&isAllowed=y; 2018.

147. Ilves I, Fagerström A, Herzig K-H, Juvonen P, Miettinen P, Paajanen H. Seasonal variations of acute appendicitis and nonspecific abdominal pain in Finland. World journal of gastroenterology. 2014;20(14):4037-42.

148. Bjork-Eriksson T, Gunnarsson M, Holmstrom M, Nordqvist A, Petruson B. Fewer problems with dry nasal mucous membranes following local use of sesame oil. Rhinology. 2000;38(4):200-3.

149. Danielides V, Nousia CS, Patrikakos G, Bartzokas A, Lolis CJ, Milionis HJ, et al. Effect of meteorological parameters on acute laryngitis in adults. Acta Otolaryngol. 2002;122(6):655-60.

150. Danielides V, Patrikakos G, Nousia CS, Bartzokas A, Milionis HJ, Lolis C, et al. Weather conditions and Bell's palsy: five-year study and review of the literature. BMC Neurol. 2001;1:7.

151. del Rio A, Trost N, Tartaglia C, O'Leary SJ, Michael P. Seasonality and incidental sinus abnormality reporting on MRI in an Australian climate. Rhinology. 2012;50(3):319-24.

152. Hox V, Steelant B, Fokkens W, Nemery B, Hellings PW. Occupational upper airway disease: how work affects the nose. Allergy. 2014;69(3):282-91.

153. Tarlo SM, Balmes J, Balkissoon R, Beach J, Beckett W, Bernstein D, et al. Diagnosis and management of work-related asthma: American College Of Chest Physicians Consensus Statement. Chest. 2008;134(3 Suppl):1s-41s.

154. Moscato G, Vandenplas O, Van Wijk RG, Malo JL, Perfetti L, Quirce S, et al. EAACI position paper on occupational rhinitis. Respiratory research. 2009;10(1):16.

155. Raulf M. Allergen component analysis as a tool in the diagnosis and management of occupational allergy. Mol Immunol. 2018;100:21-7.

156. Sin B, Togias A. Pathophysiology of allergic and nonallergic rhinitis. Proc Am Thorac Soc. 2011;8(1):106-14.

157. Bjermer L, Westman M, Holmström M, Wickman MC. The complex pathophysiology of allergic rhinitis: scientific rationale for the development of an alternative treatment option. Allergy Asthma Clin Immunol. 2019;15:24.

158. Maestrelli P, Boschetto P, Fabbri LM, Mapp CE. Mechanisms of occupational asthma. J Allergy Clin Immunol. 2009;123(3):531-42; quiz 43-4.

159. Balogun RA, Siracusa A, Shusterman D. Occupational rhinitis and occupational asthma: Association or progression? American journal of industrial medicine. 2018;61(4):293-307.

160. Airaksinen LK, Luukkonen RA, Lindström I, Lauerma AI, Toskala EM. Long-term exposure and health-related quality of life among patients with occupational rhinitis. J Occup Environ Med. 2009;51(11):1288-97.

161. Vandenplas O, Suarthana E, Rifflart C, Lemière C, Le Moual N, Bousquet J. The Impact of Work-Related Rhinitis on Quality of Life and Work Productivity: A General Workforce-Based Survey. The journal of allergy and clinical immunology In practice. 2020;8(5):1583-91.e5.

162. Kotz S, Pechtold L, Jörres RA, Nowak D, Chaker AM. Occupational rhinitis. Allergol Select. 2021;5:51-6.

163. Vandenplas O, Hox V, Bernstein D. Occupational Rhinitis. The journal of allergy and clinical immunology In practice. 2020;8(10):3311-21.

164. Meggs WJ. RADS and RUDS--the toxic induction of asthma and rhinitis. J Toxicol Clin Toxicol. 1994;32(5):487-501.

165. Ferrie JE, Vahtera J, Kivimäki M, Westerlund H, Melchior M, Alexanderson K, et al. Diagnosis-specific sickness absence and all-cause mortality in the GAZEL study. J Epidemiol Community Health. 2009;63(1):50-5.

166. Hasting RL, Merkus SL, Hanvold TN, Kristensen P, Gran JM, Mehlum IS. Impact of the Norwegian Agreement for a More Inclusive Working Life on diagnosis-specific sickness absence in young adults: a difference-in-difference analysis. BMC Public Health. 2022;22(1):235.

167. Muñoz-Murillo A, Esteban E, Ávila CC, Fheodoroff K, Haro JM, Leonardi M, et al. Furthering the Evidence of the Effectiveness of Employment Strategies for People with Mental Disorders in Europe: A Systematic Review. Int J Environ Res Public Health. 2018;15(5):838.

168. Bevan S. Economic impact of musculoskeletal disorders (MSDs) on work in Europe. Best Pract Res Clin Rheumatol. 2015;29(3):356-73.

169. Sahlstrand-Johnson P, Ohlsson B, Ahlner-Elmqvist M. Endoscopic sinus surgery improve quality of life and decrease absenteeism in patients with chronic rhinosinusitis - a multi-centre study. Clinical and Translational Allergy. 2015;5(4):O6.

170. Cheng BT, Xu M, Hassan S, Mohammed TO. Children and young adults with chronic rhinosinusitis have higher rates of chronic school absenteeism. Int Forum Allergy Rhinol. 2021;11(10):1508-12.

171. Finnish Local and Regional Authorities. Hospital Districts 2018. Available from: https://www.kuntaliitto.fi/sites/default/files/media/file/Ervat_Sairaanhoitopiirit2017_0.pdf.

172. Koskinen S, Lundqvist A. Health, functional capacity and welfare in Finland in 2011. Report 68/2012. Helsinki: National Institute for Health and Welfare (THL); 2012. Contract No.: Generic.

173. Statistics Finland: Classification of Socio-economic Groups 1989. Available from: http://www.tilastokeskus.fi/meta/luokitukset/sosioekon_asema/001-1989/index_en.html.

174. International Standard Classification of Occupations: ISCO-08 2012 [Available from: https://www.ilo.org/wcmsp5/groups/public/@dgreports/@dcomm/@publ/documents/publication/wcms_172572.pdf.

175. Statistical Yearbook of the Social Insurance Institution Finland2014. Available from: https://helda.helsinki.fi/bitstream/handle/10138/158254/Kelan_tilastollinen_vuosikirja_2014.pdf?sequence=1&isAllowed=y.

176. Buddy Healthcare Ltd Oy. Available from: https://www.buddyhealthcare.com/en/.

177. Alanne S, Roine RP, Rasanen P, Vainiola T, Sintonen H. Estimating the minimum important change in the 15D scores. Qual Life Res. 2015;24(3):599-606.

178. Richardson J, Iezzi A, Khan MA, Chen G, Maxwell A. Measuring the Sensitivity and Construct Validity of 6 Utility Instruments in 7 Disease Areas. Med Decis Making. 2016;36(2):147-59.

179. Vartiainen P, Mäntyselkä P, Heiskanen T, Hagelberg N, Mustola S, Forssell H, et al. Validation of EQ-5D and 15D in the assessment of health-related quality of life in chronic pain. Pain. 2017;158(8):1577-85.

180. Hawthorne G, Richardson J, Day NA. A comparison of the Assessment of Quality of Life (AQoL) with four other generic utility instruments. Ann Med. 2001;33(5):358-70.

181. Moock J, Kohlmann T. Comparing preference-based quality-of-life measures: results from rehabilitation patients with musculoskeletal, cardiovascular, or psychosomatic disorders. Qual Life Res. 2008;17(3):485-95.

182. Petersen KD, Kronborg C, Larsen JN, Dahl R, Gyrd-Hansen D. Patient related outcomes in a real life prospective follow up study: Allergen immunotherapy increase quality of life and reduce sick days. The World Allergy Organization journal. 2013;6(1):15.

183. Browne JP, Hopkins C, Slack R, Topham J, Reeves B, Lund V, et al. Health-related quality of life after polypectomy with and without additional surgery. Laryngoscope. 2006;116(2):297-302.

184. Piccirillo JF, Edwards D, Haiduk A, Yonan C, Thawley SE. Psychometric and Clinimetric Validity of the 31-Item Rhinosinusitis Outcome Measure (RSOM-31). American Journal of Rhinology. 1995;9(6):297-308.

185. Piccirillo JF, Merritt MG, Jr., Richards ML. Psychometric and clinimetric validity of the 20-Item Sino-Nasal Outcome Test (SNOT-20). Otolaryngol Head Neck Surg. 2002;126(1):41-7.

186. Phillips KM, Houssein FA, Boeckermann LM, Singerman KW, Liu DT, Sedaghat AR. Multi-institutional minimal clinically important difference of the 22-item Sinonasal Outcome Test in medically managed chronic rhinosinusitis. Rhinology. 2021;59(6):552-9.

187. Hytönen M H-MS, Myller J, Mäkelä M, et al. Tautikohtaisen elämänlaatumittarin validointi - esimerkkinä nenä- ja sivuontelotautikohtainen SNOT-22-mittari. Duodecim. 2017;133(13-14):1317-235.

188. Lange B, Thilsing T, Baelum J, Kjeldsen AD. The Sinonasal Outcome Test 22 score in persons without chronic rhinosinusitis. Clin Otolaryngol. 2016;41(2):127-30.

189. Erskine SE, Hopkins C, Clark A, Anari S, Kumar N, Robertson A, et al. SNOT-22 in a control population. Clin Otolaryngol. 2017;42(1):81-5.

190. Morley AD, Sharp HR. A review of sinonasal outcome scoring systems - which is best? Clin Otolaryngol. 2006;31(2):103-9.

191. Riedl D, Dejaco D, Steinbichler TB, Innerhofer V, Gottfried T, Bektic-Tadic L, et al. Assessment of health-related quality-of-life in patients with chronic Rhinosinusitis - Validation of the German Sino-Nasal Outcome Test-22 (German-SNOT-22). J Psychosom Res. 2021;140:110316.

192. de los Santos G, Reyes P, del Castillo R, Fragola C, Royuela A. Cross-cultural adaptation and validation of the sino-nasal outcome test (SNOT-22) for Spanish-speaking patients. Eur Arch Otorhinolaryngol. 2015;272(11):3335-40.

193. Lumyongsatien J, Yangsakul W, Bunnag C, Hopkins C, Tantilipikorn P. Reliability and validity study of Sino-nasal outcome test 22 (Thai version) in chronic rhinosinusitis. BMC Ear Nose Throat Disord. 2017;17:14.

194. Thakur P, Gupta V, Nanda M, Bhatia S. Psychometric Validation of Hindi Version of Sino-Nasal Outcome Test-22. Indian Journal of Otolaryngology and Head & Neck Surgery. 2021.

195. Lange B, Thilsing T, Al-kalemji A, Baelum J, Martinussen T, Kjeldsen A. The Sino-Nasal Outcome Test 22 validated for Danish patients. Danish medical bulletin. 2011;58(2):A4235.

196. Asiri M, Alokby G. Validation and Cross-cultural Adaptation of the Sinonasal Outcome Test (SNOT)-22 for the Arabian Patient Population. Cureus. 2019;11(4):e4447.

197. Koskinen A, Hammarén-Malmi S, Myller J, Mäkelä M, Penttilä E, Pessi T, et al. Translation, cross-cultural adaptation, and validation of the sino-nasal outcome test (snot)-22 for Finnish patients. Eur Arch Otorhinolaryngol. 2021;278(2):405-10.

198. Husain Q, Hoehle L, Phillips K, Caradonna DS, Gray ST, Sedaghat AR. The 22-Item Sinonasal Outcome Test as a Tool for the Assessment of Quality of Life and Symptom Control in Allergic Rhinitis. American journal of rhinology & allergy. 2020;34(2):209-16.

199. Simmonds JC, Paz-Lansberg M, Scangas G, Metson R. Endoscopic sinus surgery for chronic rhinosinusitis: 22-item Sino-Nasal Outcome Test 5-year results. Int Forum Allergy Rhinol. 2022;12(3):257-65.

200. Dizdar D, Bozan A, Dizdar SK, Göde S, Alpay HC. Evaluation of nasal symptoms in septoplasty patients using SNOT-22. Acta Otorhinolaryngol Ital. 2019;39(2):98-102.

201. Parthasarathi K, Christensen JM, Alvarado R, Barham HP, Sacks R, Harvey RJ. Airflow and symptom outcomes between allergic and non-allergic rhinitis patients from turbinoplasty. Rhinology. 2017;55(4):332-8.

202. Tomoum MO, ElSheikh MN, ElBasty H, Hagras MA, El-Naggar A. Anterior part middle turbinoplasty in endoscopic sinus surgery: a randomized controlled study. Eur Arch Otorhinolaryngol. 2021.

203. Lourijsen ES, Reitsma S, Vleming M, Hannink G, Adriaensen G, Cornet ME, et al. Endoscopic sinus surgery with medical therapy versus medical therapy for chronic rhinosinusitis with nasal polyps: a multicentre, randomised, controlled trial. Lancet Respir Med. 2022.

204. Soler ZM, Jones R, Le P, Rudmik L, Mattos JL, Nguyen SA, et al. Sino-Nasal outcome test-22 outcomes after sinus surgery: A systematic review and meta-analysis. Laryngoscope. 2018;128(3):581-92.

205. Rudmik L, Soler ZM, Hopkins C. Using postoperative SNOT-22 to help predict the probability of revision sinus surgery. Rhinology. 2016;54(2):111-6.

206. Kuan EC, Peng KA, Thompson CF, Suh JD, Wang MB. Sinonasal quality of life outcomes following laser treatment of epistaxis related to hereditary hemorrhagic telangiectasia. Lasers Med Sci. 2017;32(3):527-31.

207. Glicksman JT, Parasher AK, Brooks SG, Workman AD, Lambert JL, Bergman JE, et al. Sinonasal quality of life after endoscopic resection of malignant sinonasal and skull base tumors. Laryngoscope. 2018;128(4):789-93.

208. Bhenswala PN, Schlosser RJ, Nguyen SA, Munawar S, Rowan NR. Sinonasal quality-of-life outcomes after endoscopic endonasal skull base surgery. Int Forum Allergy Rhinol. 2019;9(10):1105-18.

209. McCoul ED, Anand VK, Bedrosian JC, Schwartz TH. Endoscopic skull base surgery and its impact on sinonasal-related quality of life. Int Forum Allergy Rhinol. 2012;2(2):174-81.

210. van Samkar A, Georgalas C. Long-term quality of life after endoscopic removal of sinonasal inverted papillomas: a 6-year cohort analysis in a tertiary academic hospital. Eur Arch Otorhinolaryngol. 2016;273(6):1433-7.

211. Leong SC, Webb CJ. Sino-Nasal Outcome Test-22 quality-of-life patterns in patients presenting with nasal septal perforation. Clin Otolaryngol. 2018;43(2):604-8.

212. Khong GC, Leong SC. Correlation of sinonasal symptoms with the size and position of nasal septal perforations. Laryngoscope. 2020;130(12):E715-e20.

213. Kang SH, Meotti CD, Bombardelli K, Piltcher OB, de Tarso Roth Dalcin P. Sinonasal characteristics and quality of life by SNOT-22 in adult patients with cystic fibrosis. Eur Arch Otorhinolaryngol. 2017;274(4):1873-82.

214. Fortunato F, Martinelli D, Iannelli G, Milazzo M, Farina U, Di Matteo G, et al. Self-reported olfactory and gustatory dysfunctions in COVID-19 patients: a 1-year follow-up study in Foggia district, Italy. BMC Infect Dis. 2022;22(1):77.

215. Lechien JR, Chiesa-Estomba CM, Hans S, Calvo-Henriquez C, Mayo-Yáñez M, Tucciarone M, et al. Validity and reliability of the COVID-19 symptom index, an instrument evaluating severity of general and otolaryngological symptoms. Acta Otolaryngol. 2021;141(6):615-20.

216. Raad RA, Ganti A, Goshtasbi K, Lehrich BM, Papagiannopoulos P, LoSavio P, et al. Temporal patterns of nasal symptoms in patients with mild severity SARS-CoV-2 infection. American journal of otolaryngology. 2021;42(6):103076-.

217. Núñez-Millán BX C-CN, Ortiz SRMJ, et al. Results of SNOT-22 in patients recovered from mild SARS-CoV-2 at 2, 3 and 4 months from diagnosis. Otorrinolaringología 2021;66(4):316-20.

218. DeConde AS, Bodner TE, Mace JC, Smith TL. Response shift in quality of life after endoscopic sinus surgery for chronic rhinosinusitis. JAMA otolaryngology-- head & neck surgery. 2014;140(8):712-9.

219. Feng AL, Wesely NC, Hoehle LP, Phillips KM, Yamasaki A, Campbell AP, et al. A validated model for the 22-item Sino-Nasal Outcome Test subdomain structure in chronic rhinosinusitis. Int Forum Allergy Rhinol. 2017;7(12):1140-8.

220. Browne JP, Hopkins C, Slack R, Cano SJ. The Sino-Nasal Outcome Test (SNOT): can we make it more clinically meaningful? Otolaryngol Head Neck Surg. 2007;136(5):736-41.

221. Dejaco D, Riedl D, Huber A, Moschen R, Giotakis AI, Bektic-Tadic L, et al. The SNOT-22 factorial structure in European patients with chronic rhinosinusitis: new clinical insights. Eur Arch Otorhinolaryngol. 2019;276(5):1355-65.

222. DeConde AS, Mace JC, Bodner T, Hwang PH, Rudmik L, Soler ZM, et al. SNOT-22 quality of life domains differentially predict treatment modality selection in chronic rhinosinusitis. Int Forum Allergy Rhinol. 2014;4(12):972-9.

223. Khan AH, Reaney M, Guillemin I, Nelson L, Qin S, Kamat S, et al. Development of Sinonasal Outcome Test (SNOT-22) Domains in Chronic Rhinosinusitis With Nasal Polyps. Laryngoscope. 2021.

224. Suominen K, Karlsson H, Rissanen A, Valtonen HM, Rasanen P, Sintonen H, et al. Perceived burden of illness in patients entering for treatment in a university hospital--is the threshold to secondary care higher for patients with depression than for those with somatic disorders? Eur Psychiatry. 2011;26(7):441-5.

225. Kluger N, Matikainen N, Sintonen H, Ranki A, Roine RP, Schalin-Jantti C. Impaired health-related quality of life in Addison's disease--impact of replacement therapy, comorbidities and socio-economic factors. Clin Endocrinol (Oxf). 2014;81(4):511-8.

226. Aro K, Back L, Loimu V, Saarilahti K, Rogers S, Sintonen H, et al. Trends in the 15D health-related quality of life over the first year following diagnosis of head and neck cancer. Eur Arch Otorhinolaryngol. 2016;273(8):2141-50.

227. Taipale K, Leminen A, Rasanen P, Heikkila A, Tapper AM, Sintonen H, et al. Costs and health-related quality of life effects of hysterectomy in patients with benign uterine disorders. Acta Obstet Gynecol Scand. 2009;88(12):1402-10.

228. Walter SD, Eliasziw M, Donner A. Sample size and optimal designs for reliability studies. Stat Med. 1998;17(1):101-10.

229. Zou GY. Sample size formulas for estimating intraclass correlation coefficients with precision and assurance. Statistics in Medicine. 2012;31(29):3972-81.

230. Rudmik L, Smith TL. Quality of life in patients with chronic rhinosinusitis. Curr Allergy Asthma Rep. 2011;11(3):247-52.

231. Fu Q, Ma J-X, Ou C-Q, Guo C, Shen S-Q, Xu G, et al. Influence of Self-Reported Chronic Rhinosinusitis on Health-Related Quality of Life: A Population-Based Survey. PLOS ONE. 2015;10:e0126881.

232. Thompson AK, Juniper E, Meltzer EO. Quality of life in patients with allergic rhinitis. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology. 2000;85(5):338-47; quiz 47-8.

233. Clinton JM, Davis CJ, Zielinski MR, Jewett KA, Krueger JM. Biochemical regulation of sleep and sleep biomarkers. J Clin Sleep Med. 2011;7(5 Suppl):S38-42.

234. Lennard CM, Mann EA, Sun LL, Chang AS, Bolger WE. Interleukin-1 beta, interleukin-5, interleukin-6, interleukin-8, and tumor necrosis factor-alpha in chronic sinusitis: response to systemic corticosteroids. Am J Rhinol. 2000;14(6):367-73.

235. Krouse HJ, Davis JE, Krouse JH. Immune mediators in allergic rhinitis and sleep. Otolaryngol Head Neck Surg. 2002;126(6):607-13.

236. Bengtsson C, Jonsson L, Holmström M, Svensson M, Theorell-Haglöw J, Lindberg E. Impact of nasal obstruction on sleep quality: a community-based study of women. Eur Arch Otorhinolaryngol. 2015;272(1):97-103.

237. Young T, Finn L, Kim H. Nasal obstruction as a risk factor for sleep-disordered breathing. The University of Wisconsin Sleep and Respiratory Research Group. J Allergy Clin Immunol. 1997;99(2):S757-62.

238. Young T, Finn L, Palta M. Chronic nasal congestion at night is a risk factor for snoring in a population-based cohort study. Arch Intern Med. 2001;161(12):1514-9.

239. Kara M, Erdoğan H, Güçlü O, Sahin H, Dereköy FS. Evaluation of Sleep Quality in Patients With Nasal Septal Deviation via the Pittsburgh Sleep Quality Index. J Craniofac Surg. 2016;27(7):1738-40.

240. Speth MM, Hoehle LP, Phillips KM, Caradonna DS, Gray ST, Sedaghat AR. Changes in chronic rhinosinusitis symptoms differentially associate with improvement in general health-related quality of life. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology. 2018;121(2):195-9.

241. Blaiss MS, Hammerby E, Robinson S, Kennedy-Martin T, Buchs S. The burden of allergic rhinitis and allergic rhinoconjunctivitis on adolescents: A literature review. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology. 2018;121(1):43-52.e3.

242. Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). Allergy. 2008;63 Suppl 86:8-160.

243. Léger D, Annesi-Maesano I, Carat F, Rugina M, Chanal I, Pribil C, et al. Allergic rhinitis and its consequences on quality of sleep: An unexplored area. Arch Intern Med. 2006;166(16):1744-8.

244. Mou YK, Wang HR, Zhang WB, Zhang Y, Ren C, Song XC. Allergic Rhinitis and Depression: Profile and Proposal. Front Psychiatry. 2021;12:820497.

245. Montnémery P, Svensson C, Adelroth E, Löfdahl CG, Andersson M, Greiff L, et al. Prevalence of nasal symptoms and their relation to self-reported asthma and chronic bronchitis/emphysema. Eur Respir J. 2001;17(4):596-603.

246. Leynaert B, Bousquet J, Neukirch C, Liard R, Neukirch F. Perennial rhinitis: An independent risk factor for asthma in nonatopic subjects: results from the European Community Respiratory Health Survey. J Allergy Clin Immunol. 1999;104(2 Pt 1):301-4.

247. Jousilahti P, Haahtela T, Laatikainen T, Mäkelä M, Vartiainen E. Asthma and respiratory allergy prevalence is still increasing among Finnish young adults. Eur Respir J. 2016;47(3):985-7.

248. Philpott CM, Erskine S, Hopkins C, Kumar N, Anari S, Kara N, et al. Prevalence of asthma, aspirin sensitivity and allergy in chronic rhinosinusitis: data from the UK National Chronic Rhinosinusitis Epidemiology Study. Respiratory research. 2018;19(1):129.

249. Håkansson K, Thomsen SF, Konge L, Mortensen J, Backer V, von Buchwald C. A comparative and descriptive study of asthma in chronic rhinosinusitis with nasal polyps. American journal of rhinology & allergy. 2014;28(5):383-7.

250. Mattila T, Hasala H, Kreivi HR, Avellan-Hietanen H, Bachour A, Herse F, et al. Changes in the societal burden caused by sleep apnoea in Finland from 1996 to 2018: A national registry study. Lancet Reg Health Eur. 2022;16:100338.

251. Strausz S, Havulinna AS, Tuomi T, Bachour A, Groop L, Mäkitie A, et al. Obstructive sleep apnoea and the risk for coronary heart disease and type 2 diabetes: a longitudinal population-based study in Finland. BMJ open. 2018;8(10):e022752-e.

252. Hui JW, Ong J, Herdegen JJ, Kim H, Codispoti CD, Kalantari V, et al. Risk of obstructive sleep apnea in African American patients with chronic rhinosinusitis. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology. 2017;118(6):685-8.e1.

253. Alt JA, DeConde AS, Mace JC, Steele TO, Orlandi RR, Smith TL. Quality of Life in Patients With Chronic Rhinosinusitis and Sleep Dysfunction Undergoing Endoscopic Sinus Surgery: A Pilot Investigation of Comorbid Obstructive Sleep Apnea. JAMA otolaryngology-- head & neck surgery. 2015;141(10):873-81.

254. Meyer VM, Benjamens S, Moumni ME, Lange JFM, Pol RA. Global Overview of Response Rates in Patient and Health Care Professional Surveys in Surgery: A Systematic Review. Annals of Surgery. 2022;275(1).

255. Jia H, Lubetkin EI. Time trends and seasonal patterns of health-related quality of life among U.S. adults. Public health reports (Washington, DC : 1974). 2009;124(5):692-701.

256. Millqvist E, Bengtsson U, Bake B. Occurrence of breathing problems induced by cold climate in asthmatics--a questionnaire survey. Eur J Respir Dis. 1987;71(5):444-9.

257. D'Amato G, Holgate ST, Pawankar R, Ledford DK, Cecchi L, Al-Ahmad M, et al. Meteorological conditions, climate change, new emerging factors, and asthma and related allergic disorders. A statement of the World Allergy Organization. The World Allergy Organization journal. 2015;8(1):25.

258. D'Amato M, Molino A, Calabrese G, Cecchi L, Annesi-Maesano I, D'Amato G. The impact of cold on the respiratory tract and its consequences to respiratory health. Clinical and Translational Allergy. 2018;8(1):20.

259. Cruz AA, Togias A. Upper airways reactions to cold air. Curr Allergy Asthma Rep. 2008;8(2):111-7.

260. Koskela HO. Cold air-provoked respiratory symptoms: the mechanisms and management. Int J Circumpolar Health. 2007;66(2):91-100.

261. Harju T, Mäkinen T, Näyhä S, Laatikainen T, Jousilahti P, Hassi J. Cold-related respiratory symptoms in the general population. Clin Respir J. 2010;4(3):176-85.

262. Muñoz-Cano R, Ribó P, Araujo G, Giralt E, Sanchez-Lopez J, Valero A. Severity of allergic rhinitis impacts sleep and anxiety: results from a large Spanish cohort. Clin Transl Allergy. 2018;8:23.

263. Buckland JR, Thomas S, Harries PG. Can the Sino-nasal Outcome Test (SNOT-22) be used as a reliable outcome measure for successful septal surgery? Clinical otolaryngology and allied sciences. 2003;28(1):43-7.

264. Poirrier AL, Ahluwalia S, Goodson A, Ellis M, Bentley M, Andrews P. Is the Sino-Nasal Outcome Test-22 a suitable evaluation for septorhinoplasty? Laryngoscope. 2013;123(1):76-81.

265. Bluyssen PM, Roda C, Mandin C, Fossati S, Carrer P, de Kluizenaar Y, et al. Self-reported health and comfort in 'modern' office buildings: first results from the European OFFICAIR study. Indoor air. 2016;26(2):298-317.

266. Aromaa AK, S. Suomalaisten työ, työkyky ja terveys 2000-luvun alkaessa, raportti 11/2010. Helsinki: The Finnish Institute for Health and Welfare; 2010.

267. Vandenplas O, Suarthana E, Rifflart C, Lemière C, Le Moual N, Bousquet J. The Impact of Work-Related Rhinitis on Quality of Life and Work Productivity: A General Workforce-Based Survey. The Journal of Allergy and Clinical Immunology: In Practice. 2020;8(5):1583-91.e5.

268. Selinheimo S, Vuokko A, Hublin C, Järnefelt H, Karvala K, Sainio M, et al. Health-related quality among life of employees with persistent nonspecific indoor-air-associated health complaints. J Psychosom Res. 2019;122:112-20.

269. Hisinger-Mölkänen H, Piirilä P, Haahtela T, Sovijärvi A, Pallasaho P. Smoking, environmental tobacco smoke and occupational irritants increase the risk of chronic rhinitis. The World Allergy Organization journal. 2018;11(1):6.

270. Runeson R, Wahlstedt K, Wieslander G, Norback D. Personal and psychosocial factors and symptoms compatible with sick building syndrome in the Swedish workforce. Indoor air. 2006;16(6):445-53.

271. Kauppinen T, Mattila-Holappa, P., Perkiö-Mäkelä, M., Saalo, Anja., et al. Työ ja terveys Suomessa: Finnish Institute of Occupational Health; 2012.

272. Hellgren J, Lillienberg L, Jarlstedt J, Karlsson G, Toren K. Population-based study of non-infectious rhinitis in relation to occupational exposure, age, sex, and smoking. American journal of industrial medicine. 2002;42(1):23-8.

273. Evans GW, Kantrowitz E. Socioeconomic status and health: the potential role of environmental risk exposure. Annu Rev Public Health. 2002;23:303-31.

274. Kela. Kelan työterveyshuoltotilasto 2019. Kela; 2021.

275. Blomgren J, Jäppinen S. Incidence and Length of Sickness Absence among Hierarchical Occupational Classes and Non-Wage-Earners: A Register Study of 1.6 Million Finns. Int J Environ Res Public Health. 2021;18(2).

276. Hansen H-T, Ingebrigtsen T. Social Class and Sickness Absence in Norway. Acta Sociologica. 2008;51(4):309-27.

277. Laaksonen M, Piha K, Rahkonen O, Martikainen P, Lahelma E. Explaining occupational class differences in sickness absence: results from middle-aged municipal employees. J Epidemiol Community Health. 2010;64(9):802-7.

278. Piha K, Laaksonen M, Martikainen P, Rahkonen O, Lahelma E. Interrelationships between education, occupational class, income and sickness absence. Eur J Public Health. 2010;20(3):276-80.

279. Daikeler J, Bošnjak M, Lozar Manfreda K. Web Versus Other Survey Modes: An Updated and Extended Meta-Analysis Comparing Response Rates. Journal of Survey Statistics and Methodology. 2020;8(3):513-39.

280. Kelfve S, Kivi M, Johansson B, Lindwall M. Going web or staying paper? The use of web-surveys among older people. BMC Med Res Methodol. 2020;20(1):252.

281. Oliveri S, Lanzoni L, Petrocchi S, Janssens R, Schoefs E, Huys I, et al. Opportunities and Challenges of Web-Based and Remotely Administered Surveys for Patient Preference Studies in a Vulnerable Population. Patient Prefer Adherence. 2021;15:2509-17.

282. Galea S, Tracy M. Participation rates in epidemiologic studies. Annals of epidemiology. 2007;17(9):643-53.

APPENDICES

Tutkimus: Miten nenän ja sivuonteloiden eri sairaudet vaikuttavat elämänlaatuun?

Esitietokaavake:

1) Etunimi: _____

2) Sukunimi: _____

3) Sosiaaliturvatunnus tai syntymäaika: _____

4) Vastauspäivämäärä: _____

5) Onko lääkäri todennut teillä aiemmin allergisen nuhan?
   Kyllä Ei

6) Jos lääkäri on todennut allergisen nuhan, mitä kohtaan teillä on todettu allergia (esim. koivu, kissa, kananmuna)?_____
   _____

7) Jos lääkäri ei ole teillä todennut allergista nuhaa, niin esiintyykö teillä kuitenkin oireita, jotka omasta mielestänne sopivat allergiseen nuhaan?
   Kyllä Ei

8) Onko teillä tällä hetkellä **tai** viimeisen kahden viikon aikana ollut allergisen nuhan oireita?
   Kyllä Ei

9) Onko teillä tällä hetkellä **tai** viimeisen kahden viikon aikana ollut akuutin/äkillisen ylähengitystietulehduksen oireita? Oireita ovat esim. kurkkukipu, nuha, korvasärky, yskä.
   Kyllä Ei

10) Tupakoitteko?

   ☐ En ole koskaan tupakoinut

   ☐ En enää tupakoi, olen lopettanut vuonna _____

   ☐ Kyllä, tupakoin

11) Jos tupakoitte, kuinka monta savuketta keskimäärin tupakoitte päivässä? _____

12) Onko teillä tällä hetkellä **tai** viimeisen kahden viikon aikana nenän limakalvot tuntuneet kuivilta?

Kyllä Ei

13) Oletteko viimeisen kahden viikon aikana käyttäneet nenän kostutusta (esim. kostutustipat, -suihke tai nenäkannu)?

Kyllä Ei

14) Onko teillä tällä hetkellä tai viimeisen kahden viikon aikana ollut käytössä **nenään paikallista lääkitystä** (esim. kortisonisuihke)?

Kyllä Ei

15) Kohdan 14 lääkkeen nimi / lääkkeiden nimet:

_____

_____

16) Onko teillä tällä hetkellä tai viimeisen kahden viikon aikana ollut käytössä **nenäoireisiin muuta kuin paikallista lääkitystä** (esim. antihistamiinitabletit)?

Kyllä Ei

17) Kohdan 16 lääkkeen nimi / lääkkeiden nimet:

_____

_____

18)Onko teillä tällä hetkellä tai viimeisen kahden viikon aikana ollut käytössä **silmäoireisiin** lääkitystä?

Kyllä Ei

19) Kohdan 18 lääkkeen nimi / lääkkeiden nimet:

_____

_____

20) Onko lääkäri todennut teillä astman?

Kyllä Ei

21) Onko teillä tällä hetkellä tai viimeisen kahden viikon aikana ollut käytössä lääkitystä astmaan tai astman kaltaisiin oireisiin (hengenahdistus, hengityksen vinkuna, pitkäaikainen yskä)?

Kyllä Ei

NENÄOIREKYSELY SINO-NASAL OUTCOME TEST (SNOT-22) **PVM** :_____
HENKILÖTUNNUS:_____

Alla olevassa luettelossa näette listan nenän ja sivuonteloiden sairauksiin liittyvistä oireista. Haluaisimme selvittää tarkemmin näitä ongelmia ja toivomme teidän vastaavan seuraaviin kysymyksiin parhaan kykynne mukaan. Ei ole olemassa oikeita tai vääriä vastauksia, vain te voitte antaa meille nämä tiedot. Arvioikaa oireenne ja ongelmanne sen mukaan kuin ne ovat olleet viimeiset kaksi viikkoa. Kiitämme osallistumisestanne.

1. Ottaen huomioon kokemanne vaivan tai ongelman vakavuus ja esiintymistiheys, arvioikaa seuraavat kohdat vieressä näkyvällä asteikolla ympyröimällä tuntemustanne vastaava numero.	Ei ongelmia	Hyvin lievä ongelma	Lievä, vähäinen ongelma	Kohtuullinen ongelma	Vakava ongelma	Pahin mahdollinen
1. Niistämisen tarve	0	1	2	3	4	5
2. Aivastelu	0	1	2	3	4	5
3. Nenän vuotaminen	0	1	2	3	4	5
4. Nenän tukkoisuus	0	1	2	3	4	5
5. Haju- ja makuaistin häiriö	0	1	2	3	4	5
6. Yskä	0	1	2	3	4	5
7. Liman valuminen kurkkuun	0	1	2	3	4	5
8. Paksun nenäeritteen määrä	0	1	2	3	4	5
9. Korvien täyteläisyyden tunne	0	1	2	3	4	5
10. Pyörrytyksen tai epävarmuuden tunne	0	1	2	3	4	5
11. Korvakipu	0	1	2	3	4	5
12. Kasvoalueen kipu/paine	0	1	2	3	4	5
13. Nukahtamisvaikeudet	0	1	2	3	4	5
14. Yölliset heräämiset	0	1	2	3	4	5
15. Unen puute	0	1	2	3	4	5

16. Aamuväsymys	0	1	2	3	4	5
17. Väsyneisyys	0	1	2	3	4	5
18. Alentunut suorituskyky	0	1	2	3	4	5
19. Alentunut keskittymiskyky	0	1	2	3	4	5
20. Turhautunut / levoton / ärtynyt	0	1	2	3	4	5
21. Surullinen	0	1	2	3	4	5
22. Hämmentynyt	0	1	2	3	4	5

SILMÄOIREET

2. Koska usein nenän ja sivuonteloiden sairauksiin liittyy **silmäoireita**, pyydämme teitä vastaamaan myös alla oleviin silmäoireita kartoittaviin kysymyksiin.

	Ei ongelmia	Hyvin lievä ongelma	Lievä, vähäinen ongelma	Kohtuullinen ongelma	Vakava ongelma	Pahin mahdollinen
1. Silmien tai silmän vetistys	0	1	2	3	4	5
2. Silmien tai silmän punoitus	0	1	2	3	4	5
3. Silmien tai silmän kutina	0	1	2	3	4	5

TERVEYTEEN LIITTYVÄN ELÄMÄNLAADUN KYSELYLOMAKE (15D©)

Ohje: Lukekaa ensin läpi huolellisesti kunkin kysymyksen kaikki vastausvaihtoehdot. Merkitkää sitten rasti (x) sen vaihtoehdon kohdalle, joka **parhaiten kuvaa nykyistä terveydentilaanne**. On tärkeää, että vastaatte **kaikkiin** 15 kysymykseen rastittamalla kustakin **yhden** vaihtoehdon.

Vastauspäivämäärä ____.____. 201_
Henkilötunnus _____

1. Liikuntakyky

1 ( ) Pystyn kävelemään normaalisti (vaikeuksitta) sisällä, ulkona ja portaissa.
2 ( ) Pystyn kävelemään vaikeuksitta sisällä, mutta ulkona ja/tai portaissa on pieniä vaikeuksia.
3 ( ) Pystyn kävelemään ilman apua sisällä (apuvälinein tai ilman), mutta ulkona ja/tai portaissa melkoisin vaikeuksin tai toisen avustamana.
4 ( ) Pystyn kävelemään sisälläkin vain toisen avustamana.
5 ( ) Olen täysin liikuntakyvytön ja vuoteenoma.

2. Näkö

1 ( ) Näen normaalisti eli näen lukea lehteä ja TV:n tekstejä vaikeuksitta (silmälaseilla tai ilman).
2 ( ) Näen lukea lehteä ja/tai TV:n tekstejä pienin vaikeuksin (silmälaseilla tai ilman).
3 ( ) Näen lukea lehteä ja/tai TV:n tekstejä huomattavin vaikeuksin (silmälaseilla tai ilman).
4 ( ) En näe lukea lehteä enkä TV:n tekstejä ilman silmälaseja tai niiden kanssa, mutta näen kulkea ilman opasta.
5 ( ) En näe kulkea oppaatta eli olen lähes tai täysin sokea.

3. Kuulo

1 ( ) Kuulen normaalisti eli kuulen hyvin normaalia puheääntä (kuulokojeella tai ilman).
2 ( ) Kuulen normaalia puheääntä pienin vaikeuksin.
3 ( ) Minun on melko vaikea kuulla normaalia puheääntä, keskustelussa on käytettävä normaalia kovempaa puheääntä.
4 ( ) Kuulen kovaakin puheääntä heikosti; olen melkein kuuro.
5 ( ) Olen täysin kuuro.

Käännä

4. Hengitys

1 ( ) Pystyn hengittämään normaalisti eli minulla ei ole hengenahdistusta eikä muita hengitysvaikeuksia.
2 ( ) Minulla on hengenahdistusta raskaassa työssä tai urheillessa, reippaassa kävelyssä tasamaalla tai lievässä ylämäessä.
3 ( ) Minulla on hengenahdistusta, kun kävelen tasamaalla samaa vauhtia kuin muut ikäiseni.
4 ( ) Minulla on hengenahdistusta pienenkin rasituksen jälkeen, esim. peseytyessä tai pukeutuessa.
5 ( ) Minulla on hengenahdistusta lähes koko ajan, myös levossa.

5. Nukkuminen

1 ( ) Nukun normaalisti eli minulla ei ole mitään ongelmia unen suhteen.
2 ( ) Minulla on lieviä uniongelmia, esim. nukahtamisvaikeuksia tai satunnaista yöheräilyä.
3 ( ) Minulla on melkoisia uniongelmia, esim. nukun levottomasti tai uni ei tunnu riittävältä.
4 ( ) Minulla on suuria uniongelmia, esim. joudun käyttämään usein tai säännöllisesti unilääkettä, herään säännöllisesti yöllä ja/tai aamuisin liian varhain.
5 ( ) Kärsin vaikeasta unettomuudesta, esim. unilääkkeiden runsaasta käytöstä huolimatta nukkuminen on lähes mahdotonta, valvon suurimman osan yöstä.

6. Syöminen

1 ( ) Pystyn syömään normaalisti eli itse ilman mitään vaikeuksia.
2 ( ) Pystyn syömään itse pienin vaikeuksin (esim. hitaasti, kömpelösti, vavisten tai erityisapuneuvoin).
3 ( ) Tarvitsen hieman toisen apua syömisessä.
4 ( ) En pysty syömään itse lainkaan, vaan minua pitää syöttää.
5 ( ) En pysty syömään itse lainkaan, vaan minulle pitää antaa ravintoa letkun avulla tai suonensisäisesti.

7. Puhuminen

1 ( ) Pystyn puhumaan normaalisti eli selvästi, kuuluvasti ja sujuvasti.
2 ( ) Puhuminen tuottaa minulle pieniä vaikeuksia, esim. sanoja on etsittävä tai ääni ei ole riittävän kuuluva tai se vaihtaa korkeutta.
3 ( ) Pystyn puhumaan ymmärrettävästi, mutta katkonaisesti, ääni vavisten, sammaltaen tai änkyttäen.
4 ( ) Muilla on vaikeuksia ymmärtää puhettani.
5 ( ) Pystyn ilmaisemaan itseäni vain elein.

Käännä

8. Eritystoiminta

1 ( ) Virtsarakkoni ja suolistoni toimivat normaalisti ja ongelmitta.
2 ( ) Virtsarakkoni ja/tai suolistoni toiminnassa on lieviä ongelmia, esim. minulla on virtsaamisvaikeuksia tai kova tai löysä vatsa.
3 ( ) Virtsarakkoni ja/tai suolistoni toiminnassa on melkoisia ongelmia, esim. minulla on satunnaisia virtsanpidätysvaikeuksia tai vaikea ummetus tai ripuli.
4 ( ) Virtsarakkoni ja/tai suolistoni toiminnassa on suuria ongelmia, esim. minulla on säännöllisesti "vahinkoja" tai peräruiskeiden tai katetroinnin tarvetta.
5 ( ) En hallitse lainkaan virtsaamista ja/tai ulostamista.

9. Tavanomaiset toiminnot

1 ( ) Pystyn suoriutumaan normaalisti tavanomaisista toiminnoista (esim. ansiotyö, opiskelu, kotityö, vapaa-ajan toiminnot).
2 ( ) Pystyn suoriutumaan tavanomaisista toiminnoista hieman alentuneella teholla tai pienin vaikeuksin.
3 ( ) Pystyn suoriutumaan tavanomaisista toiminnoista huomattavasti alentuneella teholla tai huomattavin vaikeuksin tai vain osaksi.
4 ( ) Pystyn suoriutumaan tavanomaisista toiminnoista vain pieneltä osin.
5 ( ) En pysty suoriutumaan lainkaan tavanomaisista toiminnoista.

10. Henkinen toiminta

1 ( ) Pystyn ajattelemaan selkeästi ja johdonmukaisesti ja muistini toimii täysin moitteettomasti.
2 ( ) Minulla on lieviä vaikeuksia ajatella selkeästi ja johdonmukaisesti, tai muistini ei toimi täysin moitteettomasti.
3 ( ) Minulla on melkoisia vaikeuksia ajatella selkeästi ja johdonmukaisesti, tai minulla on jonkin verran muistinmenetystä.
4 ( ) Minulla on suuria vaikeuksia ajatella selkeästi ja johdonmukaisesti, tai minulla on huomattavaa muistinmenetystä.
5 ( ) Olen koko ajan sekaisin ja vailla ajan tai paikan tajua

11. Vaivat ja oireet

1 ( ) Minulla ei ole mitään vaivoja tai oireita, esim. kipua, särkyä, pahoinvointia, kutinaa jne.
2 ( ) Minulla on lieviä vaivoja tai oireita, esim. lievää kipua, särkyä, pahoinvointia, kutinaa jne.
3 ( ) Minulla on melkoisia vaivoja tai oireita, esim. melkoista kipua, särkyä, pahoinvointia, kutinaa jne.
4 ( ) Minulla on voimakkaita vaivoja tai oireita, esim. voimakasta kipua, särkyä, pahoinvointia, kutinaa jne.
5 ( ) Minulla on sietämättömiä vaivoja ja oireita, esim. sietämätöntä kipua, särkyä, pahoinvointia, kutinaa jne.

Käännä

12. Masentuneisuus

1 ( ) En tunne itseäni lainkaan surulliseksi, alakuloiseksi tai masentuneeksi.
2 ( ) Tunnen itseni hieman surulliseksi, alakuloiseksi tai masentuneeksi.
3 ( ) Tunnen itseni melko surulliseksi, alakuloiseksi tai masentuneeksi.
4 ( ) Tunnen itseni erittäin surulliseksi, alakuloiseksi tai masentuneeksi.
5 ( ) Tunnen itseni äärimmäisen surulliseksi, alakuloiseksi tai masentuneeksi.

13. Ahdistuneisuus

1 ( ) En tunne itseäni lainkaan ahdistuneeksi, jännittyneeksi tai hermostuneeksi.
2 ( ) Tunnen itseni hieman ahdistuneeksi, jännittyneeksi tai hermostuneeksi.
3 ( ) Tunnen itseni melko ahdistuneeksi, jännittyneeksi tai hermostuneeksi.
4 ( ) Tunnen itseni erittäin ahdistuneeksi, jännittyneeksi tai hermostuneeksi.
5 ( ) Tunnen itseni äärimmäisen ahdistuneeksi, jännittyneeksi tai hermostuneeksi.

14. Energisyys

1 ( ) Tunnen itseni terveeksi ja elinvoimaiseksi.
2 ( ) Tunnen itseni hieman uupuneeksi, väsyneeksi tai voimattomaksi.
3 ( ) Tunnen itseni melko uupuneeksi, väsyneeksi tai voimattomaksi.
4 ( ) Tunnen itseni erittäin uupuneeksi, väsyneeksi tai voimattomaksi, lähes "loppuun palaneeksi".
5 ( ) Tunnen itseni äärimmäisen uupuneeksi, väsyneeksi tai voimattomaksi, täysin "loppuun palaneeksi".

15. Sukupuolielämä

1 ( ) Terveydentilani ei vaikeuta mitenkään sukupuolielämääni.
2 ( ) Terveydentilani vaikeuttaa hieman sukupuolielämääni.
3 ( ) Terveydentilani vaikeuttaa huomattavasti sukupuolielämääni.
4 ( ) Terveydentilani tekee sukupuolielämäni lähes mahdottomaksi.
5 ( ) Terveydentilani tekee sukupuolielämäni mahdottomaksi.

Kysely ”Nenä ja työ”

Nimi: _____
Henkilötunnus:_____
Vastauspäivämäärä:_____

TYÖ

1. Olen tällä hetkellä *(rengasta yksi tai useampia vaihtoehtoja)*

1 kokopäivätyössä
2 osa-aikatyössä
3 päätoiminen opiskelija
4 en ole ansiotyössä vuodesta _____alkaen
5 muu, mikä? _____alkaen

2. Mikä seuraavista kuvaa parhaiten nykyistä työtäsi: *(rengasta yksi vaihtoehto)*

1 en ole työelämässä
2 ylempi toimihenkilö (hallinto-, johto-, suunnittelu-, tutkimus- ja opetustyö yms.)
3 alempi toimihenkilö (työnjohto-, toimistotyö yms.)
4 työntekijä (teollisuus-, jakelu- ja palvelutyöntekijät yms. tuotannossa olevat)
5 kotityö, opiskelija
6 yrittäjä
7 maanviljelijä/ maatalon emäntä
8 muu, mikä _____

Jos olet ollut viimeisten 6 kk ajan pois työstä tai päätoimisesta opiskelusta, lopeta vastaaminen tähän. Kiitos osallistumisestasi!

3. Mikä on nykyinen ammattisi, työsi tai päätoiminen opiskelualasi? Vaikka et toimisi siinä nyt, merkitse viimeisin.

ammatti/ työ/ päätoiminen opiskelu

_____

vuodesta _____lähtien

4. Milloin viimeksi teit edellä mainittua työtä/ opintoja?
(Vastaa niin tarkasti kuin muistat: päivämäärä tai kuukausi ja vuosi)

_____

5. Kirjoita lyhyt tarkentava kuvaus työsi tai opintojesi tehtävistä viimeisen 6 kk ajalta:

Käännä

6. Mitä seuraavista listan tekijöistä esiintyy nykyisessä työssäsi/ opinnoissasi?
(Rengasta ja tarkenna riville mitä nämä ovat)

Mitä?

a) pöly-/ jauhemaiset hiukkaset _____
b) eläinpölyt _____
c) kemialliset aineet _____
d) liuotinhöyryt _____
e) käryt, kaasut tai huurut _____
f) kuuma ilma _____
g) kylmä ilma _____
h) ummehtunut tai homeenhajuinen ilma _____

Jos vastasit em. tekijöitä esiintyvän,
a) kuinka usein em. tekijöitä esiintyy? keskimäärin _____ kertaa viikossa

b) keskimäärin kuinka monta tuntia työpäivässä? _____ tuntia

NENÄN OIREET

7. Onko sinulla nenän oireita jotka pahenevat työssäsi/ päätoimisissa opinnoissasi?
Oireita voivat olla tukkoisuus, nenän vuotaminen, aivastelu, liman valuminen kurkkuun, kasvoalueen kipu tai paine ja hajuaistin heikentyminen.
(*Jos vastaat kyllä, merkitse mikä tai mitkä näistä oireista pahenevat vastauksesi perään)*

1 ei
2 kyllä _____

Jos vastasit kysymykseen kyllä, liitätkö seuraavia tekijöitä oireittesi pahenemiseen nykyisessä työssäsi? *(rengasta nuhaasi liittyvät tekijät)*

a) pöly-/ jauhemaiset hiukkaset
b) eläinpölyt
c) kemialliset aineet
d) liuotinhöyryt
e) käryt, kaasut tai huurut
f) kuuma ilma
g) kylmä ilma
h) ummehtunut tai homeenhajuinen ilma
i) jokin muu, mikä? _____

SAIRAUSLOMAT

8. Kuinka monta päivää olet ollut poissa työstä terveydentilasi *(sairaus, tai terveydenhoito ja tutkiminen)vuoksi* viimeisen vuoden (*12 kuukauden)* aikana?

Noin _____päivää

9. Kuinka monta päivää olet ollut poissa työstä nenän tai nenän sivuontelo-oireidesi *(sairaus, tai terveydenhoito ja tutkiminen)* vuoksi viimeisen vuoden (*12 kuukauden)* aikana?

Noin _____päivää

***KIITOS VASTAUKSESTASI*!**

KÄYTETTÄVYYSKYSELYLOMAKE

Hyvä tutkimukseen osallistuja, olet nyt täyttänyt sähköisen ja paperisen 15D-lomakkeen. Pyydän sinua nyt ystävällisesti ympyröimään jokaisen kysymyksen kohdalla omaa näkemystäsi parhaiten vastaavan vaihtoehdon numeron ja täyttämään kyselyn lopuksi taustatietosi. Vastauksesi ovat erittäin tärkeitä tutkimuksen onnistumisen kannalta.

1. Sähköisen 15D-lomakkeen käytettävyys

Miten seuraavat asiat toteutuivat **sähköisen lomakkeen** osalta? Ympyröi riveiltä omaa näkemystäsi parhaiten vastaavan vaihtoehdon numero.

Väittämät koskien sähköisen lomakkeen käyttöä	Toteutui täysin	Toteutui melko hyvin	Ei mieli-pidettä	Ei toteutunut kovinkaan hyvin	Ei toteutunut lainkaan
Sähköisen lomakkeen täyttö oli selkeää	5	4	3	2	1
Arvioin sähköisen lomakkeen tietoturvan olevan hyvä	5	4	3	2	1
Sähköisen lomakkeen täyttö oli nopeaa	5	4	3	2	1
Vastauksien muokkaus onnistui sähköisessä lomakkeessa hyvin	5	4	3	2	1
Teknologinen tai muu osaamiseni riitti sähköisen lomakkeen täyttämiseen	5	4	3	2	1
Sähköisen lomakkeen täytön aloitus ja lomakkeen palautus tapahtuivat sujuvasti	5	4	3	2	1

2. Paperisen 15D-lomakkeen käytettävyys

Miten seuraavat asiat toteutuivat **paperilomakkeen** osalta? Ympyröi riveiltä omaa näkemystäsi parhaiten vastaavan vaihtoehdon numero.

Väittämät koskien paperilomakkeen käyttöä	Toteutui täysin	Toteutui melko hyvin	Ei mieli-pidettä	Ei toteutunut kovinkaan hyvin	Ei toteutunut lainkaan
Paperilomakkeen täyttö oli selkeää	5	4	3	2	1
Arvioin paperilomakkeen tietoturvan olevan hyvä	5	4	3	2	1
Paperilomakkeen täyttö on nopeaa	5	4	3	2	1
Vastauksien muokkaus onnistui paperi-lomakkeessa hyvin	5	4	3	2	1
Teknologinen tai muu osaamiseni riitti paperilomakkeen täyttämiseen	5	4	3	2	1
Paperilomakkeen täytön aloitus ja lomakkeen palautus tapahtuivat sujuvasti	5	4	3	2	1

3. Lomakkeen valinta

Kumman lomakemuodon koit mieluisemmaksi? Ympyröi mieleisesi vaihtoehto.

1. Paperilomake 2. Sähköinen lomake 3. Ei mielipidettä

4. Kyselylomakkeiden ominaisuudet yleisellä tasolla

Seuraavaksi kysymme kyselylomakkeiden ominaisuuksista yleisellä tasolla. Minkä seuraavista lomakkeiden ominaisuuksista koet tärkeimmiksi lomakkeiden täyttöön liittyen? Ympyröi riveiltä tärkein, toiseksi tärkein ja kolmanneksi tärkein vaihtoehto. (Kultakin riviltä ympyröidään vain yksi numero.)

	Lomakkeen selkeys	Lomakkeen tietoturva ja täytön yksityisyys	Täytön nopeus	Mahdollisuus muokata vastauksia	Täyttö ei edellytä teknologista tai muuta osaamista	Täytön aloitus ja lomakkeen palautuksen sujuvuus
1. Tärkein asia	1	2	3	4	5	6
2. Tärkein asia	1	2	3	4	5	6
3. Tärkein asia	1	2	3	4	5	6

5. Vastaajan taustatiedot

Ympyröi oikea vaihtoehto tai vastaa avoimeen kysymykseen.

Henkilökohtainen tutkimuksen tutkimusnumero: _____

Syntymävuosi: _____

Sukupuoli:

1. Nainen 2. Mies

Päivämäärä: _____

Muuta kommentoitavaa tutkimukseen liittyen:

_____

_____

Kiitos osallistumisestasi tutkimukseen!