The value of the Voice Handicap Index-questionnaire and acoustic analyses to the laryngological examination.

Tom Karlsen

Thesis for the degree of Philosophiae Doctor (PhD)
University of Bergen, Norway
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1. CONTENTS

2. SCIENTIFIC ENVIRONMENT

The present study was performed at the Department of Otolaryngology/Head and Neck Surgery, Haukeland University Hospital and the Department of Clinical Medicine, Faculty of Medicine, University of Bergen.

3. ACKNOWLEDGEMENTS

The present study has been carried out at the Department of Otolaryngology/Head and Neck Surgery, Haukeland University Hospital and the Department of Clinical Medicine, Faculty of Medicine, University of Bergen.

First of all, I would like to thank all the participants who volunteered to contribute to this study. Without their benevolence, there would not be any study.

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Finally I would give a huge thanks to my wife and love of my life, for her incredible patience and understanding. Doing this work most of the time next to a full time job, has taken a large chunk of family-time thru the years. I'll be back!

Os, 2020

Tom Karlsen

4. ABBRAVIATIONS

ANOVA	Analysis Of Variance
BOTOX	Botulinum Toxin
CAPE-V	The Consensus Auditory-Perceptual Evaluation of Voice
DSI	Dysphonia Severity Index
dB	Decibel
E	Emotional
ELS	The European Laryngological Society
ENT	Ear-, Nose-, and Throat
EORTC	The European Organization of Research and Treatment of Cancer
EPI	Eysenck Personality Inventory
EPM	Endolaryngeal Phonomicrosurgery
F	Functional
F0	Fundamental Frequency
GRBAS	Grade, Rough, Breathy, Asthenic and Strain
H&N	Head and Neck
HNSCC	Head and Neck Squamous Cell Carcinoma
HUH	Haukeland University Hospital
HRQoL	Health-Related Quality of Life
Hz	Hertz

MANOVA	Multivariate Analysis Of Variance
MCT	Manual Circumlaryngeal Therapy
MDVP	Multi-Dimensional Voice Program
MPQ	Multidimensional Personality Questionnaire
MPT	Maximum Phonation Time
MTD	Muscle Tension Dysphonia
MTVD	Muscle Tension Voice Disorder
NHR	Noise to Harmonic Ratio
NLS	National Norwegian Laryngectomies
P	Physical
PROM	Patient-Reported-Outcome-Scales
PVD	Psychogenic Voice Disorder
QLQ	Quality of Life Questionnaire
QoL	Quality of Life
REK	The Regional Committee for Medical and Health Research Ethics
RFS	Reflux Finding Score
RLN	Recurrent Laryngeal Nerve
ROC	Receiver Operating Characteristic
RSI	Reflux Symptom Index
SD	Standard deviation

SLN	Superior Laryngeal Nerve
SLP	Speech-Language Pathologist
STATPED	National service for special needs education (Statlig spesialpedagogisk tjeneste).
SVEA	Stockholm Voice Evaluation Approach
TE	Thyroidectomy
UVFP	Unilateral Vocal Fold Paralysis
VAPP	Voice Activity and Participation Profile
VHI	Voice Handicap Index
VHI-30N	Norwegian version of VHI
VLS	Video Laryngostrobo-Scopy
VoiSS	Voice Symptoms Scale
VOS	Voice Outcomes Survey
VPA	Voice Profiles Analysis
VRQOL	Voice Related Quality of Life
WHO	World Health Organization

5. SUMMARY

Voice-related diseases may influence on individual’s daily life. Quantifying the extent of laryngeal pathology, voice symptoms and evaluating treatment responses for patients are challenging. The European Laryngological Society (ELS) has proposed a basis protocol for assessment of voice-related disease. Aims of this protocol include comparison of treatments of voice related diseases across cultures as well as assessing the impact of voice disorders on the health of the patient. ELS suggests to include both patient related outcome measures (PROM) and physical studies of the voice as part of assessment of voice related disease.

Voice Handicap Index (VHI) questionnaire, a validated instrument on self-reported speech challenges, was translated to Norwegian and tested psychometrically and clincially. In the first study, we aimed to study 126 voice-related disease patients and 126 controls answering the VHI-30N questionnaire. The VHI was translated to Norwegian following a formal forward-backward translation of the questionnaire from English to Norwegian. Our main finding, was that the VHI was psychometrically well functioning, and discriminated well between healthy and patients with voice disease.

In the second study, we aimed to study the ability to discriminate between voice-diagnoses dependent on disease origin, based on the VHI questionnaire. We also wanted to study the psychometrics of the VHI based on specific laryngeal diseases. The impact of different diagnoses on the VHI score, and on the cut-off values was also studied. The study was designed as a multi-center-study, including Haukeland University Hospital and Statped in both Bergen and Oslo. A total of 126 healthy subjects and 355 patients answered the VHI-30(N). We concluded that the Norwegian version of the VHI questionnaire was psychometrically well functioning, also when studied among different laryngeal disease patients specifically. When deploying large groups of patients, the VHI-30(N) had the capability to discriminate between voice-diagnoses dependent on disease origin.

The third study aimed to investigate the importance of including general Health-related quality of life (HRQoL) measures to clinical investigations. The participants (N= 80 larynx cancer, N=32 recurrent palsy, N=23 dysfunctional, N=75 degenerative/inflammation, N=19 various) were included consecutively at the laryngology clinic at Haukeland University Hospital. In addition, HRQoL data were included from one national group with laryngectomies (N=105), one group with various former HNSCC patients (N=96) and one population-based reference group (N=1956). EORTC QLQ, voice handicap index (VHI) and the Eysenck Personality Inventory (EPI) neuroticism scores were obtained in the presently recruited patient group.

A total score for global QoL/health index was calculated, in addition to scores based on function and symptoms. In particular, patients with recurrent palsy and laryngeal cancer reported decreased HRQoL. At the index levels, in particular dyspnea scores were scored dependent on larynx disease group. The VHI score correlated with the EORTC H&N35 "speech" index with a common variance about 50 %. VHI scores correlated with level of neuroticism with eight percent and EORTC scores with 22 %.

The fourth study aimed to study acoustic voice analyses, maximum phonation time (MPT) and Voice Handicap Index (VHI) in clinical investigations. The participants (N= 80 larynx cancer, N=32 recurrent palsy, N=23 dysfunctional, N=75 degenerative/inflammation, N=19 various) were included consecutively at the outpatient laryngology clinic at Haukeland University Hospital. In addition, a control group of 98 healthy subjects were included.

Voice samples, maximum phonation times (MPT) and VHI score and data on clinical examination were obtained for all participants. Based on acoustic analyses, we determined the level of jitter, shimmer and noise to harmonic ratio (NHR) as well as analyzing frequency of a prolonged vowel. The maximum phonation time was also measured.

Among larynx disease patients, acoustic and MPT analyses segregated with all determined analyses between patients and control conditions, except the dysfunctional group. But also to some extent between various patient groups. VHI scores correlated to jitter, shimmer and NHR scores among cancer and degenerative/inflammatory disease patients.

In conclusion, a thorough examination of laryngeal patients, as suggested by ELS, leads to essential information on the disease. It also forms a comprehensive basis when treatment results are evaluated.

6. LIST OF PUBLICATIONS

Karlsen T, Grieg AR, Heimdal JH, Aarstad HJ. (2012): «Cross-cultural adaption and translation of the voice handicap index into Norwegian", Folia Phoniatr Logop. 64(5):234-40. doi: 10.1159/000343080. Epub 2012 Oct 10.

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Karlsen T, Sandvik L, Heimdal JH, Hjermstad MJ, Aarstad AK, Aarstad HJ. (2017): «Health-related Quality of Life as Studied by EORTC QLQ and Voice Handicap Index Among Various Patients With Laryngeal Disease", J Voice. Mar;31(2):251.e17-251.e26. doi: 10.1016/j.jvoice.2016.07.009. Epub 2016 Aug 9.

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7. INTRODUCTION

7.1 THE VOICE

The voice is important in daily life as crucial for our oral communication, enriching social function and well-being. Voice disorders are medical conditions affecting the quality of voice production. Voice quality is described by a number of terms in different languages and the terminology is a controversial issue. Classification of voice quality should ideally be based on specifiable parameters of the voice [1].

An often used term for abnormal voice is *dysphonia*. The term is first described used in year 1706, borrowed from new Latin dysphōnia, probably from dys- dys- + -phōnia (in euphōnia euphony). Alternatively, the new Latin word could be borrowed from Greek dysphōnía "roughness of sound." The term *aphonia* was first used in year 1654 (from new Latin and Greek) from Greek aphōnia, from aphōnos voiceless, from a- + phōnē sound [2].

ANATOMY AND PHYSIOLOGY OF THE VOICE ORGAN

The larynx is positioned at the interphase between airways, esophagus and pharynx at the top of the trachea. It protects and keeps the airways open. The larynx has an advanced valve function associated with airway protection and air passage. The larynx also regulates the resistance to air passage during inspiratory and expiratory phase of the respiration [3].

The larynx plays a key role during speech as a sound transducer by producing the fundamental tone which, in the resonance space above the larynx, form the basis of the voice's sound. The sound waves come into being trough pressure changes in the airflow between the vocal folds (*rima glottidis)*. Rapid and repetitive alterations of *rima glottidis* due to wave movements (*glottic waves*) along the edges of the vocal folds create these pressure changes. The theory that has won the most support as a description of sound production in the larynx is the *aerodymanic myoelastic* theory put forward by van den Berg (Ref from 1958) [4]. This theory is based on several key elements; the *aerodynamic* principles explain how the forces acting on vocal folds develop when air from the trachea passes through the vocal tract [5]. The *myoelastic* elements ("the body and cover") refer to anatomy and physiology of the vocal folds. The outermost layer of mucosa at the vocal folds rim move smoothly over a sliding layer (*lamina propria*). Elasticity below this layer is governed by muscles and connective tissue in the vocal folds. Finally, a muscularly controlled positioning of the vocal folds is required for the vocalization [6]. When all elements are in place, sufficient *glottic waves* along the rim of the vocal folds are in place to produce voice sound. Regulation of pitch is related to tension and molding of the vocal folds, e.g. elongation and increased vocal fold tension decrease the *glottic wave* amplitudes, increase wave frequency and thereby raise the pitch.

7.2 EXAMINATION AND EVALUATION OF VOICE-RELATED SYMPTOMS

Evaluation of voice-related symptoms includes to study both the symptom(s) the patients experience related to voice production and the listeners evaluation of the voice. A patient may also be voice diseased despite normal voice sound due to intermittent symptoms, or due to the patient perceives that the voice does not work properly despite observed healthy voice function [1]. Patients with voice related symptoms are ideally examined and treated by a team consisting of, among others, of ENT doctors and speech therapists [3].

The voice quality is the result of several physiological conditions. The length, thickness and degree of muscle contraction of the vocal cords, the size of the vocal tract, the shape of the resonance space and the air from the lungs affect the quality of the voice.
The quality of the voice is most often judged by measuring deviations from the norm. The perception of a normal voice quality may, however, also vary culturally and geographically.

Fundamental registration of clinical findings and anamnestic information should basically be measured as systematic, reliable and valid as possible. The European Laryngological Society (ELS) has proposed a basic protocol for the assessment of voice disorders [7]. Such a protocol guides physicians to perform systematic examinations and offers records for patient information and collegial discussions. To apply the ELS guidelines also makes it easier to compare studies of voice-related disease across research centers. Some key principles are set as guidelines. Among these, there are five elements that should be included in the laryngological examination. These are:

1. Video-laryngo-stroboscopy which is a visual examination of vocal cord function.
2. Assessment of voice quality by listening to the voice.
3. Acoustic analyses (analyses physical deviations in the voice's sound quality and rhythm, preferably by means of both clinician and computer-based analyses).
4. Aerodynamic examinations (the simplest test is maximum phonation time).
5. Patient-reported outcome measures (PROM) for the significance of the voice-problem assessed by the individual patient.

There is no standard how voice quality should be measured, but there is some consensus in the literature that voice is a multidimensional phenomenon that include both voice quality and voice production [8]. Dejoncker's guidelines for examining vocal defects with a perceptual and acoustic analysis, video-laryngo-stroboscope, aero-dynamic examination and subjective assessment from the patient incorporate such a perspective and may therefore be used for assessment of voice quality and underlying disease [9-11].

Nest follows a more detailed presentation of the investigations that should be used according to the ELS guidelines:

7.2.1 Video-laryngo-stroboscopy

Video laryngoscopy is readily performed with standard equipment in a laryngological laboratory placed at an ENT outpatient clinic. The patients' larynx is examined either with 70 degree angle optics or with flexible instruments accessed via the nose. A stroboscopic light source gives a flashing light set to the frequency of the voice. When regulating the frequency slightly out of phase with the voice oscillations (glottic waves), one can view these fluctuations in slow motion, along the edges of the vocal folds. There is a close connection between the voice quality and the structure of the glottis waves. Furthermore, minute changes in the stretch of one vocal band can result in changes in the glottis wave. Stroboscopic light aided examination can therefore contribute to more accurate assessment of the motor movement of the vocal cords and therefore aid evaluation of the vocal cord’s function. Pertinent findings may be graded according to a method developed by Hirano modified by Bless and allied [3] which is one of the best method so far published. In short, this method involves grading irregularity in the stroboscopically generated waves; i.e. their frequency variations and variation in amplitude. The Hirano-Bless method has, however, so far not proven particularly useful in our laboratory. Video laryngoscopy will usually provide specific laryngological diagnoses. If the video recordings are stored, one can also subsequently later retrieve relevant recordings and compare any changes over time.

7.2.2 Assessment of voice quality by listening to the voice

Doing perceptual analysis of voice quality, one listen for specific voice parameters according to a pre-set definition. These parameters are often assigned to specific physiological and acoustic characteristics of the voice [12]. Perceptual analysis has been considered a gold standard for documenting voice quality; partly because voice quality can be considered a natural perceptual characteristic [13]. In addition, this method places no demands for advanced equipment. However, a main criticism of clinical use of perceptual analysis is that it is observer dependent. The perceptual analysis of voice quality is nevertheless of potentially importance, as it may provide valuable information in the investigation of the cause of voice impairment and assessment of treatment effect [13]. Instrumental measurements cannot replace auditory-perceptual analyses as shown by Dejonckere and allied [7]. Various approaches have been investigated for perceptual analysis of voice quality. One challenge with perceptual analysis in clinical work is, however, how the individual speech therapist judge the different voice parameters [14]. Perceptual analysis seems to require a lot of training by listening to different voice qualities for the individual speech therapist. When conducting studies of perceptual analysis of voice quality, there is furthermore a need for a standardized voice recording in order to define the actual scoring[7]. One usually records the reading of a standard text with about 40 seconds duration [15].

One of the first developed measuring instruments for perceptual analysis of voice quality was the GRBAS scale [16]. GRBAS was developed from Osgood's semantic scales [12] and consists of an analysis of opposite adjectives, for example, breathy - strained. Parameters considered are Grade (general assessment), Rough (roughness / irregularity), Breathy (air-filled), Asthenic (low-sounding) and Strain (excited / pressed). Scoring are from 0-3. Freitas and coworkers compared four computer programs for acoustic analysis of voices with the GRBAS form. They found the strongest correlation with Breathy, while Asthenic and Strain were the weakest [17]. The test has been used clinically in a Norwegian version by Haukeland University Hospital (HUH).

Another widespread perceptual analysis guide is Voice Profiles Analysis (VPA) [18]. VPA includes scoring of both laryngeal and supra-laryngeal voice characteristics [12]. Different parameters that are considered are hoarseness, whisper voice, scrubbing, folding / modal register, and whether the voice is tense or lax [12]. Prosodic traits, voice pitch and variation in this are also considered together with voice strength and temporal traits such as speech rate [12].

The form *The Buffalo III Voice Profile* [19] aim to assess 12 voice parameters on an interval scale from 1-5, where 1 is normal and 5 is very serious deficiency in quality. One can analyze laryngeal tone, pitch, strength, nasal resonance, oral resonance, air supply, muscles, abuse of voice, voice punch, understandable speech, and overall voice assessment.

Stockholm Voice Evaluation Approach (SVEA) is a Swedish developed form aimed at perceptual analysis. This analysis considers 26 different parameters. The form is also available in a clinical version containing 14 parameters [12]. Voice properties such as aphonia, leakage hyper- and hypofunctional, scrub, harsh approaches, unstable sound/voice, register-breakdown, and diplophonia are considered. One also measure voice and voice-power. Tveterås at Bredtvet competence center in Oslo, in close cooperation with Hammarberg with aid from Huddinge University Hospital in Stockholm, has developed a Norwegian version of this form [20, 21]. The scale, both in Swedish [15] and Norwegian [20], was first designed employing a Likert scale response pattern, but it has later been changed to 100 mm visual analogue scale (VAS) [12, 21].

The Consensus Auditory-Perceptual Evaluation of Voice (CAPE-V) [22] is another form that includes the voice parameters degree of hoarseness, screaming, leaking, pressure, voice and voice [12].

Berg has compared CAPE-V and SVEA [23] Swedish versions, and found that CAPE-V can distinguish treatment effect for patients with certain organic voice disorders, while SVEA has several parameters of clinical relevance, such as diplofonia. Berg concluded that CAPE-V or GRBAS are good alternatives if treatment effects are to be assessed. If one want to understand more of the underlying physiology behind a voice disorder, map changes in voice function over time or find acoustic correlates, a perceptual analysis form must be used that includes several specific and characteristic voice parameters for a voice disturbance. [12]. In this way the SVEA will be better. Carding, Carlson, Epstein, Mathieson & Shewell [8] has compared GRBAS, VPA and The Buffalo III Voice Profile. They recommend the clinical use of GRBAS, but find that there is still a need to further develop analytical dimensions that are realistic for clinical use, theoretically anchored, internationally accepted and have demonstrated reliability. We have started the work to implement the GRBAS test into our measurement armamentarium, but has so far not reached a level which is required in a scientific setting.

7.2.3 Acoustic analyses

Physical change in the larynx, or of motor control of the larynx will affect the acoustic character of a voice [5]. Changed voice quality may also be found in functional disease [24]. In order to study physical characteristics of the voice acoustic analysis may be performed using a computer program based on a digital audio recording [25]. The software digitizes the voice sound and gives goals for voice quality.

In this study, the program Multi-Dimensional Voice Program (MDVP) from Kay Elemetrics, USA (part of their Computerized Speech Lab suite) has been used. Among programs for acoustic analysis of voices, MDVP is widely used clinically and research wise [26-28]. Freitas and coworkers have compared four computer acoustic analysis programs, and the GRBAS perceptual observer analysis form [17]. They found a relationship that varied from weak to moderate. The variations between the computer programs were, however significant. In part due to the lack of standardization of the algorithms the different programs use, the results must therefore be viewed in the context of the chosen analysis tool.

MDVP calculates up to 33 parameters from the voice recordings, and the various parameters are considered variable valuable and reliable [7, 29-31]. ELS' protocol [7] recommends primarily the use of the *basic frequency*, *relative jitter* and *relative shimmer* as the basic acoustic measurements. These authors also point out the *harmonics-to-noise ratio* among the most "robust targets", but point out that between software for acoustic analysis it is currently inadequate standardization of this parameter. These four parameters are common parameters in acoustic analysis [27, 32]. The corresponding four parameters of the MDVP used in this study are respectively *fundamental frequency* (Fo), *jitter percent* (Jitt), *shimmer* (Shim) and *noise to harmonics ratio* (NHR).

In a review article [31] the authors studied MDVP in use together with among others Voice Handicap Index (VHI) [33]. The authors highlight the four above mentioned MDVP parameters among the nine parameters that they consider "the acoustic parameters which give the most objective information about the presence of vocal modification" [31].

Fundamental frequency (Fo).

A frequency is defined as the number of complete oscillations per second. For the voice, this means the number of complete open-close cycles of the vocal cords per second. The assigned unit is Hertz (Hz). The parameter Fo is a measure of the average voice frequency of the voice, that is, the component of the voice frequency with the lowest frequency [5]. The base frequency of the voice can also be referred to as the voice's fundamental tone. Higher frequencies related to (the product of) the fundamental frequency is called harmonies or overtones - at base frequency 200 Hz one can find harmonies of 400 Hz, 600 Hz, 800 Hz and so on. According to Traunmüller and Erikssons [34] summary of ten studies, the base frequency of the voice is average of 119 Hz (SD: 2.8) for European men and 207 Hz (SD: 2.7) for European women. Preciado, Pérez, Calzada og Preciado [35] found slightly higher fundamental frequency values in their control group. When they analyzed maintained vocal / α / with MDVP, males had 154.7 Hz (SD: 32.46) and females had 228.7 Hz (SD: 37.74).

For men, the fundamental frequency drops to fifty years before it marginally rises, while women's fundamental frequency drops until the sixties before it rises somewhat [36]. Men have more change in fundamental frequency rate during their lives than women. F0 can also vary during the day. It turns out that people who use the voice a lot during a day can have significantly higher fundamental frequency at the end of the day compared to the beginning of the day [37, 38].

Jitter percent (Jitt).

Jitter is defined as the instability of the vocal cords' wave motion [5, 25]. The Jitt parameter calculates the degree of variation from oscillation to oscillation in percent of the fundamental frequency of the voice (F0). Thus, a low jitter's score indicates smooth wave movements of the vocal cords. Jitter is also reported in some literature as frequency perturbation. In the control group in a study of Preciado and Allied , males had a Jitt score of 0.632 (SD: 0.49) and females 0.707 (SD: 0.43) [35].

Shimmer (Shim).

The amplitude is a measure of a sound's volume in decibels (dB). The Shim parameter is a percentage measure of amplitude instability and calculates the degree of variation from oscillation to oscillation of the amplitude of the voice [5, 25]. A low shimmer score indicates smooth volume in the voice. Shimmer is also in some literature referred to as amplitude perturbation. In Preciado and allied [35] control group had men a Shimmer score of 2.494 (SD: 1.11) and women 2.905 (SD: 1.65).

Noise-to-harmonics ratio (NHR).

Noise can be defined as random, aperiodic energy in the voice [5]. The NHR parameter seeks to provide a measure of noise in the voice recording [25, 36] measured in dB. This is done by the fact that sound on the recording which is not related to the fundamental frequency or its harmonics is considered noise. Since no voice is completely "clean", healthy voices will have different amount of noise, and it is challenging to define the distinction between normal and abnormal noise. Noise in the voice may have two sources; there may be a noise source near or at the vocal cords (for example, airflow through open vocal chords) or significant aperiodicity in the vocal cords' wave motion [5]. These two sources of noise may produce similar acoustic effects, and thus be difficult to distinguish between based on how it sounds, but the presence of noise will separate both from healthy voices. NHR gives a ratio value where low score (near 0) indicates low noise and high score (near 1) indicates a lot of noise. Preciado and allied [35] states the following NHR values for their control group: males had 0.132 (SD: 0.025) and females had 0.127 (SD: 0.21). Freitas and allied found that of the above parameters, shimmer and NHR had the best predictive value compared to jitter. The variation between different software programs were also substantial [17].

7.2.4 Aerodynamic examination - maximum phonation time

For the aerodynamic approach, the maximum phonation time (MPT) of the held vowel / a / which has the longest duration for each informant is measured. MPT provides a simple value in seconds for how long a person can produce a continuous sound. MPT is according to the ELS' [7] protocol the simplest and most widely used aerodynamic parameter. Poor closing of the vocal cords will cause short MPT since the air in the lungs cannot be used effectively during expiration. There has been shown a relationship between MPT duration and pathology in the larynx [39].

7.2.5 Patient-reported outcome measures (PROM)

Several different instruments have been developed for quantitative PROM related to voice disease. One of the most internationally used measuring instruments is:

- Voice Handicap Index (VHI) [33], and short versions of this:
    - Voice Handicap Index-10 (VHI-10) [40]
    - Voice Handicap Index-9 (VHI-9) [41].

Developed by a group at the Henry Ford Hospital in Detroit VHI consists of 30 statements (items) that can be divided into 3 sub-scales each including 10 statements:

Emotional, Functional and Physical [33]. The informants consider the extent to which each statement (item) fit themselves by putting a ring around this answer option derived as a Likert scale: never (0), almost never (1), sometimes (2), almost always (3) and always (4). VHI is the most widely used laryngology PROM questionnaire today. It has been translated into many languages with validity and reliability tested and found satisfactory. Verdonck-de Leeuw et al. [42] has compared the results from VHI in several different languages: English (US), English (UK), German, French, Dutch, Italian, Portuguese, Belgian and Swedish and found them psychometrically satisfactory. In addition, this questionnaire has been translated into among other languages Chinese [43], Spanish [44] and Arabic [45]. In recent years has Persian [46] and Latvian [47] been added. A formal presentation of some of the different translations of the VHI has been presented in table 1.

Other PROM instruments in use are;

- Voice-Related Quality of Life (VRQoL) [48]

VRQoL was developed staring with patient interviews. The test consists of 10 questions that can be divided into two subgroups; 1) socially-emotional and 2) physically-functional. Several questions in this questionnaire and VHI are similarly formulated.

- Voice Symptom Scale (VoiSS), [49]

VoiSS includes 30 questions. The aim was to develop and validate a patient-derived battery with questions aimed at voice symptoms, which can be used as a sensitive assessment tool in order to assess reported voice pathology, and to capture perceived changes among voice-diseased patients in clinical everyday life.

- Voice Activity and Participation Profile (VAPP), [50].

This test consists of 28 questions divided into five subgroups; self-perceived severity of the voice problem, impact on work, impact on daily communication, impact on social communication and emotional impact.

- Voice Outcomes Survey (VOS), [51].

The test consists of five questions with five response options. It aims to measure disease-specific health conditions in people diagnosed with recurrent palsy.

All the above mentioned instruments have been found to be valid and reliable studied in the original language. Franic and allied compared 9 of these PROM tests [52]. Of these, 4 were selected for a more comprehensive review: VHI, VAPP, V-RQOL and VOS. These instruments were evaluated based on 11 measurement standards related to item-information, versatility, practical use, breadth and depth of health goals, reliability, validity, and sensitivity. Both VHI and V-RQOL met 7 of the 11 criteria, but VHI performed better on item-information, practical use and reliability compared to V-RQOL, while V-RQOL showed higher sensitivity compared to VHI. Agency for Health Care Research and Quality reported in 2002 that VHI met their strictest criterion for reliability, validity and availability of normative data [53]. There is a need for Norwegian translations of the above mentioned tests. Two of the tests have been translated into Norwegian: Voice Handicap Index (VHI-30N) [54] and Voice-Related Quality of Life (V-RQOL) [55]. Formally reporting about the translation of VHI into Norwegian, as well as psychometric testing of this translation has been the initial study in this thesis.

An additional important question is to what extent VHI scores differently between different laryngological diseases. Several studies have used VHI scores to show the effect of laryngological treatment [56-58] (Table 1). If VHI may be used as such, VHI should ideally distinguish between less and more serious laryngeal diseases. It may further be assumed that the cut-off value of the VHI between healthy subjects and laryngeal diseased may be affected by their specific diagnosis. These are current unanswered questions that are well suited for scientific studies, and are therefore among the hypotheses that are raised in current thesis.

7.3 Quality of Life

7.3.1 Quality of life term

Historical development

The term quality of life (QoL) is often used in daily life [59]. In the everyday language, the term may have different content, such as being satisfied with life, well-being, happiness, meaning and functional status[60].
Within a scientific approach to HRQoL, Morton [61] has given a historical overview upon which the following is based:

One of the earliest definitions associated with the concept of QoL is related to Aristotle (384-322 BC). He used terms such as perceiving "the good life", "successful" or "being happy". But what constitutes happiness can be discussed. Aristotle also states that happiness was a state of feeling or a type of activity [62].

Hippocrates (~ 460-377 BC) realized that a patient's satisfaction with life and psychological well-being was important for coping with disease, but in general, the traditional medical perspective was mainly to cure disease, and the patient's psychological concern was of little interest. Voltaire (1694-1761) commented on the doctors' lack of interest in the general well-being of patients: "Doctors are men who prescribe medicine that they know little about, to cure diseases they know less about, in humans, which they do not know anything about".

Illness will obviously affect QoL. The phenomenon was already recognized by Lichtenberg (1742-1799), who stated that "the feeling of health is obtained only through illness". But in general, the QoL was rarely mentioned in medical scientific literature up to the 20th century. Specific QoL in relation to patients' health came at a later point.

Definition & Content of the Quality of Life concept

A question of interest has also been how the QoL concept can be related to specific symptoms that have been caused by an illness, or focus on the general well-being of the individual. The Department of Mental Health of the World Health Organization, WHO (1995)[63]defines QoL as: "an individual's perception of their position in life in the context of the culture and value systems they live in and in relation to their goals, expectations, standards and interests". This definition is general. Other researchers regard high QoL as the subjective evaluation of the good and satisfactory life as a whole [64]. The same is supported by Gotay and Moore [65], who defined QoL as the experience of well-being composed of two components: the ability to carry out daily activities that reflect physical, psychological, and social well-being, and the patient's satisfaction with the degree of functioning and control of disease. The same type of definition has also been supported when QoL was defined as an individual's total satisfaction with life and general perception of personal well-being [66].

Ferrans [67] has focused on what the important part of the QoL of an individual is, by defining QoL as: "a person's perception of well-being derived from satisfaction or dissatisfaction with the areas of life that are important to him/her ". On the other hand, other defined QoL has to represent the functional effect of a disease and its treatment on the patient [68]. Today, both approaches are often represented in the tests used.

Many have also argued that an operational definition is preferable. QoL is measured with a specific questionnaire which then defines QoL. Which quesitions to include, can obvioussly be discussed. Consequently, it is possible to build a specific, empirical definition. Examples of such empirical definitions are by Padilla and co-worker [69], which defined HRQoL as: "a personal, evaluative statement summarizing positive or negative traits that characterize a psychological, physical, social, and spiritual well-being. a time when health, illness, and treatment conditions are relevant ”. Many of the QoL-instruments used today have major influence from this approach.

Several researchers have suggested that QoL can be a multi-level construction. Spilker [70] suggests these three levels:

1. Total assessment of well-being.
2. Wide domains (ie Physical, physiological, economic, spiritual, social).

3. Components of each domain.
These levels underline the complexity of the concept of QoL.

It is obvious that observed from the outside, a person with seemingly low QoL can have an excellent QoL based on his or her own assessment. This has been formulated as "the gap" theory [71]. The gap is the difference between current experience on the one hand and perceived goals on the other [72]. QoL may also be formally stated as the gap between patients' expectations and achievements. The smaller the gap, the higher the QoL [72]. Such a suggested QoL definition is: "The perception of the discrepancy between the reality of what one has and what one wants or waits constitutes the QoL" [69, 73]. The same mindset is also emphasized in the WHO's QoL definition, which states that QoL is the patient's perception of their position in life in the context of culture and value systems in which they live, and in relation to their goals, expectations, standards and interests [63].

It has also been shown empirically that QoL scored by health personnel can give significant differences compared to the assessment by the patient him or herself [74-76]. Today, there seems to be general agreement that QoL is a matter of personal self-scoring judgement [71, 77].

7.3.2 General Quality of Life Measures

In recent years, there has been an increasing number of studies on QoL in patients after undergoing treatment for various diseases. One area of interest is the QoL of patients who have been successfully treated for head & neck cancer [78-81]. At the ENT department, Haukeland University Hospital (HUH), one has systematically studied the QoL of successfully treated head & neck cancer patients over a fifteen year period [82-84]. Some of these patients have laryngological disease in the sense of laryngeal cancer. The findings made for head & neck cancer patients in general, are also shown to be valid for laryngeal patients with a cancer disease. It will therefore be of interest to study to what extent HRQoL findings made for laryngeal cancer patients also apply to patients with other laryngeal disease.

We aim to use "The European Organization of Research and Treatment of Cancer" (EORTC) questionnaire to measure general QoL (EORTC-QLQ-C30) in this study, based on previous experience with the form in head & neck cancer patient studies at ENT department, HUH [85-87]. This questionnaire can also be used for diseases other than cancer [88]. Using this questionnaire for other diseases will also broaden the knowledge base for QoL in cancer.

7.3.3 Symptom-specific Quality of life Measures

The EORTC QLQ system assumes that, in addition to general QoL, the disease-specific HRQoL should also be measured. We have chosen to use EORTC QLQ H & N35 [89] targeting head-neck cancer patients. The head & neck section consists of fourteen symptom items that are presented in eighteen questions and eight function items that are presented in twelve questions. Descriptive items about pain, nutrition and weight are also included. The head & neck-specific part is developed in Norway. Relevant questions from this test can also be asked patients with benign laryngeal disease.

It has been found that there is little correlation between perceived QoL and expected sequels after undergoing treatment [90]. What has been found, however, is that personality traits and the choice of coping strategy are of importance for the QoL judgement in patients after having undergone head & neck cancer treatment. Such results are based on collected values for the QoL quality, personality traits, coping methods and level of social support in all patients who were successfully treated for head & neck cancer at the ENT department, HUH [79, 85, 91].

VHI is considered a Patient-Reported Outcome Measures (PROM). It is not clear to what extent VHI overlaps with classical QoL questionnaires. Lundstrøm and allied have studied the association between VHI and EORTC score levels in patients who had undergone laryngectomy, and found that these complement each other well [92].

VHI may therefore be studied in relation to an established QoL measuring instrument. This has a goal included in the current thesis. As such it is of interest to study to what extent personality traits affect the VHI score, and this is one of the objectives of the current thesis. It is furthermore of interest to compare the reported QoL of patients with laryngeal disease with scores from the population as a whole.

7.4 The Personality Aspect

Historical development

Personality has been studied scientifically for more than a century; scientifically since Freud introduced psychoanalysis around 1900 [93]. Psychoanalytic theory has a psychodynamic, clinical approach to personality. Two sets of levels are important as structural concepts: deliberate, conscious, and unconscious. The other concept level is related to id, ego, and superego.

Individuals go through different stages of development, according to Freud [93]. The oral, anal and phallic steps have been a focus of psychological personality development as well as research regarding these questions. The psychoanalyst Erikson also expanded the vision to cover psycho-social development. Early experience, especially the four to five first years of life, is important in the Freudian theory when it comes to personality development [93].

Many early analysts extended the Freud theory frame. Adler emphasized social aspects, while Jung generalized more on life energy than specific sexual energy. Others emphasized cultural factors and interpersonal relationships. Clinical development in psychoanalysis has recently focused on self-definition and self-esteem. The Freudian theory seems, howver, to suffer from being ambiguous, with unclear defined terms, and difficult to test in relation to specific hypotheses [93].

The trait concept has been supported by various psychologists. Eycenck suggested that people have extensive predisposition to respond in particular ways, which were called character traits [94]. He claimed that the personality had a hierarchical structure with a specific response level, a habitual level, trait level and super-factor level, as for Eysenck, for example, was extroversion or neuroticism. Allport believed that character traits represented basic units in the personality and defined them based on characteristics such as frequency, intensity and scope of situations [95].

The three-factor theory of Eysenck is based on factor analysis. He found two basic dimensions of personality and called them introversion - extroversion and neuroticism [94]. He also later added a third dimension, psychoticism [96].

Cattell also had a factor-analytical approach to character traits. He distinguished among three methods: bivariate, multivariate and clinical studies of the personality. Cattell was interested in the correspondence between behavior and personality, but also focused on motivational processes. In addition, he used the term state to refer to mood and emotional change. Examples of conditions are anxiety and depression [97].

Character theorists such as Allport, Eysenck and Cattell agree on the presence of broad personality dispositions, but they differ in other approaches. Allport is critical to factor analysis, but Eysenck and Cattell use it. They also disagree with the number of character traits in the description of the personality. It is, however, among contemporary character theorists a development toward consensus around "The Big Five" dimensions [93].

Critics of character theory emphasize that human behavior is variable. Some also argue that the importance of situational influences should be emphasized. This has been called the person-situation controversy. There is evidence of longitudinal stability of the traits, also over extended periods of time [98]. Although personality can change, it is forces that work to maintain personality stability over time. In addition, there is considerable evidence that neuroticism is determined by genetics [99].

Definition

In order to define the term personality we can ask how the term is used in our daily lives. It deals with continuity, stability or consistency about what a person does, believes or experiences [100]. This is also how Pervin and John define personality: "Personality represents the characteristics of the person explaining consistent patterns of feeling, thinking and behavior" [93]. Or it can be defined as McCrae & Costa (in Wiggins, 1996): "A system defined by personality traits and the dynamic processes through which they affect the psychological functioning of individuals" [98].

The personality five-factor model, has been developed for over fifty years [101] and is still considered a contemporary valid theory [102]. According to the five-factor model [103], personality can be perceived as divided into:

1. Neuroticism: Neuroticism is an emotional factor. The people who score high on this tend to be emotionally insecure people who are chronically anxious.

2. Extraversion: Extraversion assesses quantity and intensity of interpersonal interaction, activity level, need for stimulation and capacity for joy. An extraverted person is person-oriented, optimistic, likes to have fun and loving. People with low scores on this are reserved, sober, task oriented and quiet.

3. Openness to Experience: This has to do with culture. High scoring people are curious with broad interests, creative and untraditional. The low scoring person is conventional, with narrow interests and non-analytical.

4. Agreeableness (pleasure): This is the opposite of hostility and irritability. This trait reflects a continuum from compassion to resistance in thoughts, emotions and actions. An Agreeable person is person-oriented, optimistic, likes to have fun and loving, good-hearted, nice and helpful. The low-scoring person is characterized as being cynical, rude and manipulative.

5. Conscientiousness: The factor reflects the will to achieve something and to be accountable. The trait is related to people's degree of endurance in goal-oriented behavior. The highly scoring person is characterized as being hard-working, self-

disciplined and ambitious. The low-scoring person is characterized to be pointless, careless and unwilling.

Eysenck Personality Inventory (EPI)

Eysenck Personality Inventory (EPI) is one of the most widely used and used tests in the field of personality research. It is a questionnaire consisting of fifty-five questions / statements. Eysenck originally published a test that was to measure neuroticism and extra-introversion along with a lie scale [104]. He later added a psychoticism scale to the test [96]. Neuroticism (twenty four questions), extra version (twenty-four questions) and the lies (nine questions) are dimensions of Eysenck personality inventory [104] based on the informants responding YES or NO to each question in accordance with their own perception of it their self. The scales are calculated as sum score. The test has been translated into Norwegian, and is well documented in relation to validity and reliability [105].

It has been performed limited scientific work to investigate the connections between voice impairments and personality, but in 2000 Roy and allied published a work comparing personality traits measured with "Multidimensional personality questionnaire". Multidimensional Personality Questionare (MPQ) in a control group and four groups of patients with different voice-related ailments (functional dysphonia, nodules, spastic dysphonia, and vocal cords). They found that there was a clear difference between the groups in terms of personality traits. Functional dysphonia was related to introverted personality, stress reactions, alienation and depression to a greater extent than the other diagnostic groups. Nevertheless, there was no clear connection between personality and negative effect on voice-related ailments [106].

7.5 Voice disorders

It is common to divide the voice disorders into broad categories; organic, functional and neurological, based on the causal factors [107].

Organic factors are pathological processes, injury or disease, interrupting the function of the vocal cords or the laryngeal mucosa [3]. Neurological voice disorders are often included into the organic category referring to conditions affecting the neurological control of laryngeal structures via the afferent or efferent nerve signals [3].

Functional voice disorders often refers to ailments that patients relate to voice use without any identifiable physical cause following thorough clinical examination of the larynx. The patient may than be unable to utilize a normal functioning larynx to create a normal voice [12]. Functional disorders are heterogeneous and emotional. Psychological factors play a role in some such patients. Functional voice disorders are more common than organic difficulties as patients consulting speech therapists [107, 108]. The separation between organic and functional voice disorders may be diffuse [109, 110]. A functional disorder can lead to organic changes in the larynx, such as when nodules arise from excessive and incorrect use of the voice [9].

There is no reliable overview of the incidence of voice disorders in Norway. According to a study by Grieg [111] including consecutive patients referred to the speech therapist at Statped west in Bergen and Statped south-east in Oslo, the distribution of diagnoses was as follows: about 3/5 parts functional, about 1/5 organic and 1/5 with uncertain diagnosis, most of which have probably an organic cause. Speech therapist Elstad performed a study in 1998 based on 250 subsequent clinical examinations of patients referred to speech therapy. She found based on this material that about half of the patients had functional disorders, while the other half was distributed on various organic causes.

7.5.1 Organic voice disorders

According to definition, organic voice disorders are due to conditions that affect the voice production i.e. the phonation [9]. Any condition or disease affection the function of the larynx may cause disturbances of vocalization (dysphonia/hoarseness) and/or affect the respiratory function causing dyspnea [5]. Organic voice disorders may be due to congenital or acquired disorders. They may be due to muscle injuries or paralysis or damage to the nerve-pathway to the larynx.

As already mentioned, neurological causes are sometimes presented as a separate group. These voice disorders are caused by disturbances of either the central or peripheral nervous system [107]. Neurological disorders affecting corticospinal-fibres, cerebellum, basal ganglia and upper and lower motor neurons may cause voice problems [112]. Other causes for neural disturbances may be surgery or trauma [5]. When the signalling system does not function properly, control of the motor planning and control of the muscles is impaired or even lost.

The treatment for organic voice disorders is primarily medical or surgical. Some conditions may also benefit from pre- or postoperative speech therapy. Examples of such conditions are nodules, and other types of abnormal growth where voice use may play a causative role [5, 107]. Speech therapy can also help following injury and trauma [5].

Cancer

Laryngeal cancer may affect the voice production as an organic voice disorder, especially when located at the vocal folds.

The prevalence of laryngeal cancer varies from country to country [113]. Estimates from 2009 show 12,290 new cases of laryngeal cancer and 3,660 deaths due to this type of cancer globally [114]. Tobacco smoking is the major risk factor for laryngeal cancer [113, 115, 116]. Other causes may include alcohol and working environment with, for example, a lot of dust from asbestos, gases and chemicals [5, 12]. It is significantly more men than women who develop laryngeal cancer in most countries [113, 117]. The incidence among women has increased concurrent with the increase of female smokers [114]. The most common cancer type in the larynx is squamous cell carcinoma of the vocal folds (glottis cancer). The second most common tumour location is cranially to the vocal folds (*supraglottic*). Tumours under the vocal folds (*subglottis*) are rare, normally estimated from 1% to 5% of the larynx cancer cases [12, 113, 114].

The primary symptom of glottic cancer is hoarseness. A Finnish study of 312 patients showed that hoarseness also was the most prominent symptom of supraglottis cancer, but also common to subglottis cancer [113] [2, 68, 69, 72]. If the tumour is localised supra- or subglottically, it may develop more than glottic tumours before the symptoms appear. Other common supraglottic symptoms are globus laryngus, sore throat, dysphagia, and pain by swallowing. If the tumour is large (at any location) it can cause breathing difficulties [5, 12].

It is often hoarseness that causes the doctor consultation when the cancer is detected. At an early stage of glottic cancer, the cancer Appears like a whitish, irregular thickening of the vocal cords. If the tumour has developed and grown into the muscle tissue, it can lead to reduced vibrations in the vocal cords [12].

The change of voice quality in patients suffering from laryngeal cancer depends on the size and location of the cancer. Tumours outside the vocal cords will not necessarily lead to a changed voice [5]. Acoustic targets such as jitter, shimmer and noise can reflect fundamental aperiodic vibrations in the vocal cords caused by the cancer. Several studies have noted increased disturbances in frequency and amplitude with cancer [5, 118, 119]. Colton found slightly higher basic frequencies for the vowel / α / and / e / in male patients with T1 and T2 carcinoma and much higher baseline rates for the vowels in female patients with T1 glottical cancer compared to control conditions. The variation in pitch increased for male patients with T1 and T2 cancer [5].

Increased noise levels have also been found on in patients with laryngeal cancer, especially in the higher frequency ranges [5]. Measurement of noise in the voice energy may indicate the severity of cancer. A study of 57 patients showed that Noise-to-harmonic was pathological of in 77% of T1 cases and all T2-T4 cancer cases studied [5].

The sub-location of a malignant laryngeal tumour may play a role as to risk for metastases. There are few lymphatic vessels around and below the vocal folds. In the case of glottis and subglottic cancer, the risk of spreading to lymph nodes is less than that of tumour superior to the vocal cords. [114].

Radiation therapy used to treat laryngeal cancer usually produces side effects that last from a few months to many years. The mucous membranes of the larynx may become irritated and cause infections, including fungal infection. The mucous membranes of the oral cavity and the pharynx may become brittle and dry, leading to pain and swallowing difficulties, as well as hoarseness. Late radiation side effects can be oedema and fibrosis in connective tissue, as well as reduced salivary gland function with secondary dry mouth. This can lead to speech impairments and reduced phonation ability [12].

A recently published study compared treatment with radiation and laser surgery in patients with T1a glottis cancer compared by voice handicap index (VHI), perceptual and acoustic analysis, aero-dynamic examination or stroboscope examination. The postoperative voice was air-filled in both groups. The group treated with radiation also tended to have a “harder” voice with higher values for jitter in acoustic measurement. No difference was significant between the treatments, and the results did not show which method ended up with the best voice quality [120].

A similar study from 1994 found similar results for perceptual and acoustic analysis, as well as subjective assessments. Laser surgery tended to produce slightly better results compared to voice quality, but the observed differences between treatment methods were not significantly different [121]. A study done at the ENT department at Haukeland University Hospital also found no significant difference in voice quality when comparing radiation and surgery using endoscope evaluation [122]. Other studies have shown similar results [114].

Reinke`s edema

Fluid accumulation in the vocal cords, in the Reinke`s space (the outer layer of lamina propria), is called Reinke`s edema. The entire length of the membranous vocal cord becomes oedema-like and swollen [123]. The fibres of the elastic system of the outer layer participate in the vibration of the vocal cords. They contribute to the mucous membrane of the vocal cord having fluid elasticity. When aging, these fibres become naturally larger and coarser, and the elasticity decreases, which causes the voice to change. These changes can be observed in people with Reinke`s oedema, and may be part of the cause of change in voice following Reinke's edema [124]. The variation and organization of fibre proteins also seems to be important for Reinke`s space associated optimal vocal folds function [125].

Reinke`s oedema is a relatively common disorder of the vocal cords, and the prevalence in patients with vocal defects varies from 5.5% to 7.7%. [126]. Women are affected more often than men, and the disorder mostly occurs in people over 40 years of age [127].

The main symptom of this oedema is that the voice's fundamental frequency becomes lower [125]. The oedema increases the mass of the vocal cords, causing more slowly vibrations. This gives a deeper, hoarser voice. The vocal closure can become incomplete, and one gets a dysphonic voice that sounds rough and scrubbed [128, 129]. Female voices that are affected by Reinke`s oedema often acquire the characteristics of a male voice [125].

Cigarette smoking is recognized as a common cause of this disorder [123, 125, 127]. Misuse and too extensive use of the voice can also cause oedema. Reflux, allergy and laryngeal disease may also have an impact on this condition [130].

Recurrent palsy

Recurrence palsy is a paralysis with reduced or deficient ab-and adduction of one or both vocal folds due to damage to the Recurrent Laryngeal Nerve (RLN). Defect function of the Superior Laryngeal Nerve (SLN) does not affect the vocalization as much because the motoric neurons of the SLN to the crico-thyroid muscle regulate elongation and tightening of vocal folds, and not the ad- and abduction. SLN is placed deep in the neck which protects it from damage, and it is most commonly the RLN that is affected [131]. It is most common with a unilateral vocal cord palsy [129]. Palsy has the consequence that the vocal cords may not acquire the normal phonation position [129]. This leads to hoarseness and possibly difficulty breathing if the nerves are damaged on both sides [5]. Following insufficient glottis closure the air used during phonation is used quicker with consequently short phonation time from one expiration. One may also having difficulty lifting heavily, as one cannot keep the air trapped in the lungs in order to stabilize the torso during such physical efforts [132].

The RLN follows a circuitous route, arising from the vagus nerve in the upper mediastinum and then ascending to the larynx in the tracheoesophageal groove. On the right side the nerve curves around the subclavian artery. On the left side the nerve curves around the aortic arch [3]. The RLN is located close to the thyroid gland [129] and is therefore vulnerable to surgical damage both in the thoracic cavity and around the thyroid gland [133, 134].

Diseases such as thyroid cancer, diseases in oesophagus, aorta aneurisms, respiratory tract diseases and lymph node diseases may all affect the function of the nerve. Vocal cord palsy may also be caused by inflammation of the nerve, or a trauma to the nerve as a consequence of, for example, an accident. If the cause for RLN palsy remain not specifically determined the condition is denominated Idiopathic RLN palsy [135].

Laryngitis

Laryngitis is a collective term for inflammation in the larynx and vocal cords [5]. The inflammation is often caused by a bacterial or viral infection associated with colds or sore throats [136], but can also be due to allergies [137], voice overload [138] and smoking [139]. The main symptom of laryngitis in adults is hoarseness or loss of voice, regardless of aetiology. The condition may be acute or chronic [5].

7.5.2 Functional voice disorders

Functional voice disorders are a heterogeneous group of conditions that can be divided into several subgroups e.g. psychogenic voice disorder (PVD) and hyper-functional or muscle tension voice disorder (MTVD) [108]. In clinical practise functional voice disorders are often related to "improper" use of the larynx and vocal folds in order to produce voice. This can cause tension in the (*intrinsic*) muscles involved in vocal folds movements or (*extrinsic*) muscles around the larynx, regulating the positioning of the larynx. The voice may be affected through excessive use, for example in professional use or through communication in noisy environments. Extensive clearing and coughing can also affect the voice [9, 107].

Psychogenic causes like stress or emotional factors are recognized to affect the voice and may cause a voice problem to develop or worsen [9, 108, 140].

The term Muscle Tension Dysphonia (MTD), first used by Morrison, Nichol and Rammage [141] has been used to describe those voice disorders resulting from laryngeal muscle hyper-function without structural changes to the vocal folds. Its onset could be sudden i.e. when cheering at a sporting event, or gradual i.e. developing over the course of months or years. MTD could occur following an upper airway infection, or as part of one's unique personality. It can affect pitch, loudness and quality or a single component of voice. It could result in aphonia when the tense folds are abducted or dysphonia when they are adducted. It may be disabling to the speaker or merely a nuisance. It can be further aggravated by medical conditions or develop as a compensatory response to another underlying problem. In short, the speaker is incorrectly using muscles for voice production, causing changes in the acoustic signal and sensory complaints. Common causes of MTD are overuse, i.e. abuse, and misuse of the larynx and vocal folds. Various medications, chronic medical conditions, i.e. reflux, and ongoing exposure to irritants contribute to the problem, as do changes in emotional and physical health. The most common voice characteristics are roughness, breathiness and strain, with accompanying pitch and phonation breaks, and hard glottal attacks. Phonation range may be reduced or show evidence of a break. Complaints of vocal fatigue, throat irritation and dryness, and an increased desire to clear the throat are frequent. Likewise, visible and palpable signs and symptoms of excessive musculoskeletal tension in the upper torso and larynx may be present. Voice therapy may be effective in reducing or eliminating MTD. Length of treatment varies widely, with gradual onset, long-standing MDT usually requires more therapy than sudden-onset aphonia or dysphonia [142].

8. AIMS OF PRESENT STUDIES

I To document a Norwegian translation of the Voice Handicap Index (VHI), evaluate reliability and validity of the VHI-30N, and to investigate whether a shortened VHI questionnaire can be recommended.

II To investigate in a multicenter setting the ability of the VHI to discriminate between different voice diseases, the psychometrics of VHI dependent on specific voice disease and the influence the exact voice diseases regarding best VHI cut-off values between the healthy and diseased.

III To investigate HRQoL among patients with voice disease and to study the relation between HRQoL and present neuroticism.

IV To further document the importance of acoustic voice analyses and maximum phonation time measures into clinical investigations.

9. STUDY DESIGN, SUBJECTS AND METHODOLOGY

9.1 Design

This thesis is based on an observational combined cross-sectional and case-control survey design using quantitative methodology. The study included standardized clinical tests by examination of patients in conjunction with outpatient visit. Patients were interviewed and informed individually by one researcher during the consultations and answered questionnaires in equal manners afterwards. The study was conducted by using self-reporting questionnaires that had been translated into Norwegian language and used in previous studies [90, 143, 144].

9.2 Etichs

The ethical guidelines of the Helsinki Declaration (World Medical Association, 2000) form the ethical basis of this work. The Regional Committee for Medical and Health Research Ethics, Western Norway (REK-Vest), approved the project. Written informed consent was obtained from all participating patients and controls, and they were informed they could withdraw from the study at any time, without any consequences. They were given the opportunity to ask questions about the study and their participation at any time by contacting the project leader. Anonymity was ensured and the data securely stored.

9.3 Subjects

Subjects from 7 different cohorts have been included in the 4 studies of this thesis. The total number of patients are 555, of these 459 had at the time of inclusion medical conditions recognized to affect the voice, or they were previously treated for such conditions. Among these were 104 laryngectomies. Former HNSCC (96) patients may have altered voice function due to location of disease (larynx) or treatment (i.e. surgery or radiotherapy) of disease in other locations.

In total 232 controls were included in two different cohorts to match patients included in paper 1, 2 and 4 (see table below). Finally in paper 3 answers to PROM from 1956 randomly selected citizens of Norway were included as controls.

Cohorts used in different papers:				
Cohorts	Paper 1	Paper 2	Paper 3	Paper 4
IA	x	x		
IB	x	x		
I/II		x	x	x
HUH/HNCC			x	
GNR			x	
NLS			x	
HUH/control				x

Cohort IA: Controls (N=126) used in paper I and II

Cohort IB: Patients (N=126) used in paper I and II

Cohort I/II: Patients (N=229) used in paper II, III and IV

Cohort (HUH/ HNSCC): Former HNCC Patients (N=96) used in paper III

General Norwegian references (GNR): Control (N=1956) used in paper III

Cohort of National Norwegian Laryngectomies (NLS) (N=104) used in paper III

Cohort (HUH/control): Controls (no-voiced disorders) (N=106) used in paper IV

Paper # 1

This study consists of two cohorts:

Controls, also Cohort IA in paper #2.
The control group (N=126) consisted of 29 men (median age 53, range 20-68) and 97 women (median age 46, range 19-66) who were recruited among psychology students, primary school teachers, special educational needs teachers, consultants, secretaries and speech-language therapists. Participants in the control group were anonymous and the included did not receive any compensation for their participation.

Patients, also Cohort IB in paper #2.
A total of 126 adult patients participated in the study: 35 men (median age 49, range 29-83) and 91 women (median age 44, range 18-77). The patients were examined and assessed for voice diseases for the first time in one of two centers: the Norwegian Support System for Special Education, Statped Vest in Bergen or Statped Sør-øst in Oslo.
Some patients included in the study were self-referred; others were referred via the Pedagogical- Psychological Service. The patients originated from most areas of Norway. All patients were examined by an ENT specialist, and the diagnosis they received was reported by the patients when included in the study. Both patients and controls signed consent forms before they were included in the study.

Paper # 2
This study consists of three cohorts:

Cohort IA (controls) and Cohort IB (patients) as in paper # 1.

Cohort II (patients), also Cohort I in paper # 3 and paper # 4.
The participants (N = 229) consisted of 138 men [median age 61 years (range 24–86 years)] and 91 women [median age 51 years (range 18–79 years)], and were included consecutively following consultations at the laryngology clinic in HUH when studied, including stroboscopic investigation of the vocal folds. Patients with benign disease were included before specific therapy was initiated. The dysplasia and cancer patients were included at follow-up after completion of primary therapy. The patients were

required to answer intelligibly to written questions in Norwegian in order to be included.

Paper # 3

This study consists of four cohorts:

I: Cohort of Haukeland University Hospital (HUH) patients
with voice disease, also Cohort II of paper # 2 and Cohort I of paper # 4.

II: General Norwegian reference

A randomly selected sample of 3000 people, reflecting the age and gender distribution of the adult Norwegian population, was obtained by a random draw from the adult Norwegian population. Of the 3000 invited, 1956 returned the questionnaire and were available for analyses. The EORTC QLQ-C30 (version 2.0) and a questionnaire about demographic data and health were mailed. Detailed information about these reference HRQoL data has been published previously [145, 146].

III: Cohort of patients from HUH formerly treated for head and neck squamous cell carcinoma (HNSCC)

This group included 96 successfully treated patients with HNSCC from western Norway aged less than 80 years who were primarily treated at HUH. HRQoL data were collected a median of 4 years after the primary diagnosis of HNSCC. The patients with HNSCC responded to the questionnaires by structured interviews. The patient, tumor, and therapy characteristics have been published previously [144].

IV: Cohort of National Norwegian Laryngectomies (NLS)

All patients with laryngectomy in Norway become members of the NLS, a subsidiary of the Norwegian Cancer Society. Copies of EORTC QLQ-C30 (version 3.0) were mailed to all registered members of the NLS below 80 years of age. A second invitation was mailed if the patients did not respond to the first. In total, 104 patients answered the questionnaires, and the specific data have been published previously [147]. The vast majority of these patients were laryngectomized owing to cancer of the larynx.

Paper # 4

Cohort (cohort I) of Haukeland University Hospital (HUH) patients with voice disease.

Control group (HUH/control)

The control group consisted of 106 volunteers recruited by information posters and letters distributed to employees and students at the hospital and university. The inclusion criteria were that a signed informed consent, age above 18 years, a video-laryngo-stroboscopy, and a successfully recorded voice sample and answered the VHI questionnaire. Furthermore, cognitive functions and language skill needed to answer the VHI questionnaire intelligible were required. If the controls were diagnosed with larynx pathology at the video-laryngo-stroboscopy they were excluded from the study. Eight participants were excluded either due to findings of pathology in their larynx, did not complete the examination or had missing parameters in the VHI questionnaire. This constitutes 8.5 % dropout, and a total of 98 participants were included in the study, median age 34 year and range 19-74 years. Thirty-tree males, median age 32 year, range 19-63 years, and 65 women, median age 35 year, range 22-74 years were included.

9.4 Methods

In paper I the diagnostic was based on an ENT examination of the patients before referral to speech therapy.

In paper II-IV the diagnostic procedures of each patients were based on clinical examination with both speech therapist and laryngologist. The video-recordings (from VLSS) were analyzed systematically according to methods modified from those described by Hirano and Bless [16]. The mobility of vocal folds and glottic waves were noted and any pathological conditions in the laryngeal mucosa i.e. causes of organic voice disorders were described.

The speech therapist could assess the voice quality by listening to the voice both during examinations and voice recordings.

Voice recordings were performed with each patients sitting in a small sound-proof room to reduce noise disturbances. The recordings were standardized by a fixed distance from mouth to microphone (40 cm). The patient read a standard text from a Fable, including a sustained vowel (*a*) as long as the patient`s breath could maintain.

The voice recordings were stored in separate files for further analysis. Acoustic analyses were performed with soft-ware delivered by Key-Elemetrics (USA). Selected acoustic parameters; Fundamental frequency, Shimmer, Jitter, Noise to harmonics ratio were measured.

The maximum phonation time could be measured from the voice recordings and used as a substitute for respiratory function tests or "aerodynamic" examination.

Each patient was given a handout with standardized questionnaires including Patient Related outcome measures (PROM) in order to assess the significance of the voice-problem for the individual patient. For more details see appendix.

9.5 Statistical analyses

Statistical significance was considered if $p<0.05$. All p-values reported represent two-sided tests for all four papers.

Paper # 1

Chi square, correlation analyses, and Receiver Operating Characteristic (ROC) analyses were employed as indicated. The VHI-30, as well as the abbreviated scales as published by Nawka et al. [18] and Rosen et al. [19] have been calculated from the same data.

Paper # 2

Cronbach's alphas, analysis of variance ANOVA analyses followed by Bonferroni post hoc method, as well as percentiles were calculated as indicated. In particular, the post hoc part of the ANOVA analyses was used to discriminate between various laryngological disease group scores as recommended by Holm and Christman [22].

Paper # 3

Cronbach alpha, Pearson correlation, partial correlation, and multivariate analysis of variance (MANOVA) analyses followed by *post hoc* Bonferroni method were calculated as indicated.

Paper # 4

Cronbach alpha, Pearson correlation, linear regression analysis and Multiple Analysis of Variance (M) ANOVA analyses followed by post hoc tests (Bonferroni method) were calculated as indicated.

10. RESULTS AND SYNOPSIS OF PAPERS

10.1 Paper # 1

The aims of the first study was to examine the psychometric properties of a Norwegian translation of the Voice Handicap Index (VHI) and test its ability to discriminate between patients and controls. In addition, potential abbreviated versions of VHI were studied. Following standard translation, 126 healthy subjects and 126 patients with laryngeal disease answered the Norwegian translation of the VHI-30 (hereafter, VHI-30(N)). The VHI(N) showed a high Cronbach's alpha. One three-level question where the subjects rated level of voice disease correlated well with the VHI(N) scores. Differences between patient and control groups were significant for all questions of the VHI(N). Receiver Operating Characteristic (ROC) analyses demonstrate that the Functional, Physical, Emotional and total VHI scores discriminated very well between patients and controls. Good discrimination was also found when analyzed the abbreviated scales as published by Nawka et al and Rosen et al. This Norwegian version of the VHI questionnaire seems to be psychometrically sound.

10.2 Paper # 2

The aim of this study was to determine to what extent the Voice Handicap Index-Norwegian (VHI-N) was scored depending on specific laryngological diseases. In a multi-center study, 126 healthy subjects and 355 patients with different voice-related diseases answered the VHI-N. The VHI-N scores showed high Cronbach's alpha. Analyses of variance were performed with VHI-N dependent and specific voice-related disease as independent variable, and showed highly significant dependence by group allocation. When studying post hoc analyses secondary to this ANOVA analysis, we have shown that the control group scored lower than the entire patient groups except the dysplasia group. Aphonic patients scored worse than all the other groups except those with spasmodic dysphonia. The cancer patient group furthermore scored better than patient groups with recurrent palsy, dysfunctional disease and spasmodic dysphonia. In addition, patients with recurrent palsy scored worse than patients with degenerative/inflammatory disease. No influences of patient age, gender, or smoking were observed in the VHI-N scores. The VHI-N is a psychometrically well-functioning instrument, also at disease-specific levels and discriminates well between health and voice diseases, as well as to some extent between different voice-related diseases. The VHI-N may also be recommended to be studied when monitoring voice-related disease treatment.

10.3 Paper # 3

The third study aimed to document the importance of including general HRQoL measures to clinical voice disease investigations. The participants (N = 80 larynx cancer, N = 32 recurrent palsy, N = 23 dysfunctional, N = 75 degenerative/inflammation, N = 19 various), were included consecutively at the laryngology clinic at Haukeland University Hospital. In addition, HRQoL data was included from a national group of laryngectomy patients (N = 105), from a group of former HNSCC patients (N = 96), and from a population-based reference group (N = 1956). Obtained were the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ), the Voice Handicap Index (VHI), as well as the Eysenck Personality Inventory (EPI) neuroticism scores from the patients group with patients with specific voice disease. By analysis of variance, we have determined significant dependence of groups analyzing the sum global QoL/health index, the functional HRQoL sum score, and the symptom sum HRQoL scores. In particular, patients with recurrent palsy and laryngeal cancer had lowered HRQoL. At the index levels, in particular dyspnea scores, were scored depending on larynx disease group. The VHI score correlated with the EORTC H&N35 “speech” index with a common variance of 52%. VHI scores correlated with level of neuroticism with 8% common variance and EORTC scores with 22%. Our conclusion was, in particular, among patients with voice-related disease, those with recurrent palsy and laryngeal cancer had lower HRQoL. Furthermore, the HRQoL and VHI scores were inversely tied to neuroticism among the patients in the specific voice disease group.

10.4 Paper # 4

The fourth study aims to investigate the relationship between aerodynamic measurements, acoustic measurements from voice analyzes and VHI-30N, and further documenting the importance of acoustic voice analyses and maximum phonation time measures into clinical investigations. : The participants (N= 80 larynx cancer, N=32 recurrent palsy, N=23 dysfunctional, N=75 degenerative/inflammation, N=19 various) were included consecutively at the outpatient laryngology clinic at Haukeland University Hospital. In addition, a control group of 98 healthy subjects were included. Obtained were voice samples, maximum phonation times (MPT) and the Voice handicap index (VHI) scores in addition to standard clinical information. Acoustic analyses were performed from these samples determining level of jitter, shimmer and noise to harmonic ratio (NHR) as well as analyzing frequency of a prolonged vowel. The maximum phonation time was also measured.
We found Jitter, shimmer and NHR scores correlated strongly to each other. By ANOVA analyses, we have determined significant dependence on diagnostic group analyzing all the obtained acoustic scores. All patient groups but the dysfunctional group scored to some extent differently from the control group. In addition, jitter scores differed between dysfunction and recurrent palsy and shimmer score differed between dysfunctional and cancer group. Regarding NHR the cancer patients scored

higher than the degenerative/ inflammatory group. Dependent on MPT, the cancer group scored higher than the degenerative/inflammatory and recurrent palsy groups. Among larynx disease patients acoustic and MPT analyses segregated with all determined analyses between patients and control conditions except the dysfunctional group, but also to some extent between various patient groups. VHI scores correlated to jitter, shimmer and NHR scores among cancer and degenerative/inflammatory disease patients. Acoustic analyses potentially add information useful to laryngological patient studies.

11. DISCUSSION

Methodological considerations concerning strengths and limitations

Inclusions:

Inclusions in general: Ideally the inclusion criteria should have been identical throughout all studies of this thesis and more patients should have been included in order to obtain a better differentiation between specific diagnoses. Still, the total numbers of patients sums up to a total of 555 and the controls to a total of 2188 which are substantial numbers. These large numbers provided information as to voice function and QoL and provided information for comparison between cohorts in a matter that would have been difficult to achieve with less patients.
Controls: Three different control groups were used in the four studies included in this thesis as shown in the table in chapter 9.3. In paper I and II the 126 controls were recruited mainly among students and teachers. The controls reported no voice disease and the voices were also controlled by speech therapists using perceptual voice assessment as method. The patient and control groups were well matched regarding gender and age in study I. It is regarded as strength of these two studies that the controls were thoroughly selected, but ideally controls should have been matched towards patients also in study II.

The references (GNR) in study III have previously been published by Hjermstad and co-workers [145], who examined the HR-QoL in general Norwegian population. The reference group (GNR) consisted of 1956 answers (EORTC QLQ 30) from 3000 invited subjects randomly drawn from the Norwegian population including subjects from 18 to 93 years of age. The questionnaires included questions regarding speech, experience of voice disease as well as level of voice use at home and at work. It is valuable to have information as to these voice related health questions from such a large representative group of the population.
The controls of study IV were 98 volunteers recruited at the hospital (HUS). They were between 22 and 74 years of age (median 34 years) and thus younger than the patients (median 51, range 18-79). It is possible that older controls, e.g.

patients with non-laryngeal diseases, would have matched the patients better. Interestingly, the patient group with dysfunctional disease scored similar to the control group indicating that in the limited sense of acoustic variables this group may be viewed a "control" group adding support to the actually denominated control group the age difference is not of any major importance.

Patients: The 126 patients from cohort 1B used in study I and II were included after examination by ENT physician and referred to assessment for speech therapy. The design of the first two studies could have been improved if the diagnoses had been obtained from an ENT examination for all patients and not from reports of the patients.
The cohort I/II used in study II, III and IV consisted of 229 patients that were included consecutively after examination by laryngologist and speech therapist. The thorough examination by two specialists and precise diagnostic procedures including high return-rate (81 %) are recognized as strengths of these studies concerning data from this cohort. This also involves cohort HUH/HNSCC consisting of 96 patients successfully treated for HNSCC included in study III.
The cohort of NLS used in paper III consisted of 104 patients and has been included in a former study by Birkhaug and colleagues (2002). This was a relatively homogenous group of patients as the majority of them were laryngectomized due to laryngeal cancer.

Diagnostic categories:
When the VHI total score was analyzed in the third study patients were grouped according to specifically clustered larynx diseases [148]. This was done based on a method suggested by Verdonck- de Leeuw et al [42] and Nawka et al [41].
The most versatile group of these was *degenerative/ inflammatory and dysfunctional;* including dysplasia, laryngitis and papilloma subsequently merged with Reinke edema, polyps and cysts as shown in figure 2 and table 2 in paper III. It can be discussed whether important information is lost when diagnostic groups are allocated in categories, and not presented as strictly separated clinical entities. Still,

from a clinical view it is interesting to note that 95% CI VHI total score (fig. 2 paper III) show such a linear increase from controls (lowest) to aphonia (highest), with cancer patients at the lower part compared to the other disease groups. This is an intriguing observation as one would expect that cancer patients should give high VHI scores due to such a serious disease. Most cancer patients were included after successful treatment of their disease which possibly have influenced their answers concerning voiced related problems. It is from this observation pertinent to argue that VHI has a disease specific QoL aspect that should be taken into account when used in clinical settings.

Standardization of Voice analyses:

A general problem faced by all researchers using acoustic voice analyses is the lack of standardization across laboratories. Computer software [149, 150], and the individual voice laboratory standard methods differ. This hampers the ability to compare results from different centers. In fact, various results may to some extent be caused merely by lack of standardization of the analyses. In this thesis all voice recordings were performed in the same location under strictly repetitive conditions. Still our findings must be judged according to the test situation described.

11.2 Discussion of the main findings of the study

Voice Handicap index as diagnostic tool

Abbreviated version of VHI: Several authors have suggested that the number of items included in the VHI could be reduced [41, 151]. This thesis has revealed that VHI has a strong internal consistency across different domains and discriminate well between patients and controls. Furthermore, an abbreviated version of VHI may be used as an alternative to the standard version. Abbreviated questionnaires revealed scores closely correlating to the original VHI-30, and abbreviated VHI are less time consuming and can be used in clinical practice and possibly also in research.

Disease dependent VHI score: VHI was developed in order to quantify perception of voice disease in general, and not primarily to separate between various laryngological diseases [33]. In the recent years many investigators have extended the scope of VHI. In fact scores may depend on disease-groups as shown also in this thesis. A grading of six disease-related scoring levels from low to high is suggested for VHI-N. Lowest scores were obtained with voice-related cancer, then structural/inflammatory larynx disease, dysfunctional disease, recurrent nerve disease, spasmodic dysphonia and finally aphonic patients.

By comparing VHI scores from different patient-cohorts valuable information can be achieved as to how different diseases affect voice. But there are some obstacles with these comparisons. The rating of VHI scores and voice related diseases differs between studies. In addition splitting of laryngeal diseases into groups differs as well. This may be one explanation for various findings. Rosen et al. [152] have suggested that highest VHI scores is obtained from patients with unilateral vocal fold paralysis, followed by patients with benign vocal fold lesions. Helidoni et al. [153] and Lam et al. [43] have determined in their studies that the neurogenic group had the highest VHI scores, whereas the lowest scores occurred in the inflammatory group. Verdonck-de Leeuw [42] and Nawka [41] suggested larynx-diseased patients to be placed in five different groups having similar levels of VHI scores; i.e., dysfunction, nodules, structural, palsy and laryngitis reporting from a multi-center study based on data from many different sites across Europe. More studies are needed in order to sort out a more consistent relation between laryngeal disease and voice handicaps as measured by VHI. This thesis has also shown that measurements of general QoL can add valuable information to this relation. The voice may be a good index of the general state of health including mental health [1].

Acoustic parameters as diagnostic tool

Quality of voice is difficult to assess in an objective way as stated earlier in this thesis. One would expect that a standardized and objective measurement of the specifiable parameters of voice production would be helpful. Analyses of acoustic parameters are therefore recommended by Dejonckere and co-workers in the ELS protocol [7]. This thesis has shown that objective measurements of acoustic parameters enables a differentiation between subjects with no voice problems and patients with affected voice. As could be expected the controls and patients with functional diseases could not be separated by analyses of acoustic parameters. The voice in functional diseases does not differ substantially from a normal voice.

The parameters jitter, shimmer and NHR differentiated best between the laryngological diagnoses and one can therefore argue that these should be included in objective analyses of voice quality when used in a clinical setting. Interestingly jitter, shimmer, and NHR scores correlated closely as shown in this thesis. This is in accordance with the findings of Ziwei and allied [154]. These parameters thus seem to reflect a common underlying entity. It is therefore interesting to note that there was a 10% common variance between VHI scores and the acoustic variable scores among the patients; mostly among cancer and degenerative and inflammatory patients.

It is well known that pitch level and pitch range of the voice depend on growth and aging process (Zemling 1998). Age of the patients may therefore be of importance as to acoustic analyses [155, 156]. This has also been shown in the present study regarding jitter, shimmer, and NHR.

Prior to puberty there is little difference in pitch and range of the voice when boys and girls are compared. After puberty there is an anatomical difference between the male and female larynx resulting in a drop of the lower range of male voice with about one octave [1]. Therefore the influence of gender on the voice must be taken into account when voice parameters are measured. In this thesis acoustic measurement absolute values were generally scored different among males and females as have been shown previously [157, 158]. Adjusting by age and gender did however not remove significant results regarding jitter, shimmer, and MPT on diagnostic group measured by ANOVA analyses. Gender did on the other hand influence on the significant differences concerning the F0, therefore separate analyses dependent on gender were conducted. Larger studies are needed in order to determine more conclusively the importance of age and gender as to acoustic analyses dependent on diagnosis.

Studies in this thesis have shown that acoustic voice analyses reveal pathology of the voice when laryngeal diseases are studied on group level. The magnitude of voice pathology is also reflected to some extent. Analyses of jitter, shimmer and NHR can provide important objective information as to voice quality for example when treatment effects are studied. This is in accordance with observations from Gillespie and co-workers [159].

Patient-reported outcome measures (Prom)

Voice disorders and quality of life aspects:

This thesis shows that HRQoL scores may yield information when included in clinical routine laryngological consultations.

Level of neuroticism is known to have a major impact on HRQoL scores in various patient groups [144]. Thus, it is of relevance to determine this impact when acquiring HRQoL of patients with larynx disease. We have shown that level of neuroticism was correlated to the HRQoL scores and to VHI scores with a substantial common variance. In addition, some of the common variance between the HRQoL and the VHI scores were secondary to level of neuroticism. The impact of neuroticism on the VHI scores in addition strengthens the view that the VHI score may be classified as a HRQoL score.

Among the patients with larynx disease, the EORTC-H&N35 "speech" index in particular was scored with a close association to the VHI score. This suggests that the VHI questionnaire may be used generally in conjunction with the EORTC QLQ. This is especially important when the EORTC-H&N35 speech index is scored with a high value.

The association between voice quality and general HRQoL suggests that voice patency contributes substantially to the generation of good HRQoL. Therefore voice-improving treatments may be used in order to generate better HRQoL among patients with larynx diseases.

Patients scored HRQoL differently depending on type of laryngeal disease. Recurrent palsy and laryngeal cancer is associated with low general HRQoL. The low HRQoL of cancer patients could be expected. It is therefore interesting to notice that laryngectomized, who particularly must be expected to suffer from the sequels [147], scored similar to patients of other disease groups.

Many patients with recurrent nerve palsy have serious diseases [160], therefore low HRQoL scores are not surprising. The larynx has an important a protective and respiratory role as valve, therefore [160] respiratory function may be reduced in these patients. Rosen et al [152] have accordingly found that among patients with larynx disease, worst VHI scores were obtained from those with unilateral vocal fold paralysis. Helidoni et al [153] and Lam et al [43] have shown similar findings in their studies. Patients with neurogenic diseases affecting the larynx had the worst VHI scores. The present results, together with the above mentioned studies, support that patients with recurrent palsy as a group suffer from reduced HRQoL.

The low HRQoL, as well as the possibility of underlying and more serious illness in recurrent palsy patients indicates that thorough examination looking for causality of the palsy as well as treatment of this condition should be prioritized. Whether efficient treatment e.g. by medialization of vocal folds also improves HRQoL should be studied further.

Clinical appliances of VHI/Prom and acoustic analyses

The VHI-N patient scores were obtained in a setting indicating that valid VHI scores may be obtained in standard clinical settings. The VHI-N discriminated excellent between healthy and laryngological disease [54], and VHI discriminated between laryngological disease groups. On the other hand, to use individual test results to sort between specific voice-related diseases should be done with caution.

This thesis shows that HRQoL scores may yield information when included in clinical routine laryngological consultations. Some of the differences between the groups reached 10 HRQoL points, which is consistent with being of important clinical relevance [161]. A general HRQoL questionnaire will provide additional information about the patient and is therefore recommended to be included as part of a complete investigation of patients with voice disease.

12. CONCLUDING REMARKS AND FUTURE PROSPECTS

Through this study we have shown a Norwegian version of the VHI questionnaire to be a psychometrically functioning instrument, also at disease-specific levels. VHI-N discriminates well between healthy and voice diseased, as well as between some voice-related diseases. Furthermore, when viewing VHI in relation to HRQoL measures, in particular, among patients with voice-related disease, those with recurrent palsy and laryngeal cancer had lower HRQoL. Furthermore, both the HRQoL and the VHI scores were inversely tied to neuroticism. The VHI-N and a general QoL questionnaire may be recommended to be used when monitoring voice-related disease treatment. Among larynx disease patients acoustic and MPT analyses segregated with all performed analyses between patients and control group except the dysfunctional group. VHI scores correlated to jitter, shimmer and NHR scores among cancer and degenerative/inflammatory disease patients. Acoustic analyses potentially add information useful to laryngological patient studies.

We have in this thesis performed an observational combined cross-sectional and case-control survey design using quantitative methodology. The patients have only been examined when they were included in the study, but not been followed over time. It would be of value to perform a similar study with a longitudinal design included. As always, an investigational design with many successive measuring points will improve the value of the data. This would e.g. have allow a firmer conclusion about reliability of the different measurements presently obtained.

Of the parameters listed in the recommendation of ELS to be included in the laryngeal examination, we have investigated the relationship between PROMs, aerodynamic analysis and acoustic analysis. All patients and controls have in addition been examined by an ENT doctor with videolaryngostroboscopy. The result beyond diagnosis of videolaryngoscopy has not been included in this thesis. In the case of perceptual analysis, we did try to perform it with a limited number of patients and controls, but we were not successful.

Ideally, quantitative measurements about the voice quality obtained from the laryngoscopic investigations have a potential to improve the knowledge of the actual state of larynx. No such sensitive scores has been generally accepted. Such a score should be developed, e.g. in line with the development of the CLE scoring scheme as published previously by our group [162]. Computer-assisted analysis of vocal cord movement with the aid of stroboscopic light during phonation may also improve the results obtained from investigation as the one presently reported. Laryngeal electromyography during phonation may also hold promises to contribute to voice investigation as has been shown especially concerning vocal cord paralysis [163].

As stated above, we did not from acoustic analyses using the GRBAS form [164, 165] obtain results that gave meaningful results when included into formal statistical analyses. To develop this concept further into a useable concept that could be included to studies like the present may improve the quality of future studies like the ones presently reported. Therefore, it should be a future aim of similar investigations as the one presently performed with addition of clinician-based voice analyses.

Obviously, the studies often improve in quality by using multicenter approach during data acquisition. Preferably, this should also have been done using patients with different mother tongue languages. To investigate this would have improved the quality of the conclusions of the study.

We have used the EORTC QLQ out of many choices as the HRQoL general questionnaire. It is possible that other such questionnaires could have given other conclusions as to QoL of the included subjects. A more thorough personality test, like the MMPI, than the presently used could also have generated a more faceted picture of how the QoL may be generated in laryngology patients.

Design-wise an experimental treatment study including the present measurements could bring valuable information about the instruments presently used. To study the investigated parameters in a treatment frame where the patients were scored before and after a specific treatment would obviously have improved the validity of the results [165, 166]. Several investigators have tried this. Ohlsson and allied did a randomized clinical trial to study the voice therapy outcome, i.e. measured by VHI, comparing individual therapy, group therapy and no therapy [167]. They showed an improved VHI score following voice therapy, as well as improved voice quality as measured by speech language therapists. The study included randomization to different treatments, but the study was not blinded. Abrahamsson and allied have reported measured effect of voice therapy by VHI pre-post intervention on group and individual therapy and found improvement [168]. This illustrates that high quality studies are performed and published concerning treatment of vocal cord disorders with e.g. voice therapy. To add acoustic voice analyses to such studies would help to circumvent the challenge with eliminating placebo effects from such results.

Professional use of voice as e.g. with singers represents an interesting area of research, in particular when larynx-related disease affects such patients. To use systematically a formal battery of tests like presently performed in such situation could both answer more about validity of the ELS design currently investigated, and possibly show an area where a more systematic approach concerning voice patients could be useful [169].

One interesting option is to use instant biofeedback from both laryngoscopic examination and/or acoustic analyses as learning help for patients with mal-functioning vocal box. The patient could focus on generating as little shimmer as possible, or generating a smooth stroboscopic vocal cord wave without actually be given any extra information. If successfully, this could be another example of useful clinical biofeedback [170].

Several of the disease groups included to the present study could have been studied in more detail. In particular, this holds true with the patients with laryngeal cancer. The question about voice quality following cancer surgery compared to radiation therapy when treating patients with limited laryngeal cancer is still controversial and still needs input of knowledge [171].

In any case, we have studied voice investigation tools that may be included to the voice analysis tool box, but this subject matter still needs to be more studied. One present main focus has been to validate the suggested voice investigation strategy as originally suggested by ELS [10], and it is supported that QoL scores and acoustic analyses at group level may be included to standard voice studies. Future studies, ideally placebo controlled treatment studies, must further validate the present findings.

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14. APPENDIX

Questionnaires employed in the study:

- Demographic data
- Voice Handicap Index (VHI)
- EORTC QoQ-30
- H&N-35
- Eysenck Personality Inventory (EPI)

Tables:

- Table 1

Hvordan opplever du din stemmevanske?

- Sett kun **ett** kryss ved svaralternativet som passer deg og skriv der det er nødvendig -

---

1. Kjønn:
   - ☐ kvinne
   - ☐ mann

2. Født, årstall:______________

3. Når oppstod stemmevanskene dine?
   Prøv å angi omtrent årstall: ______________

4. Angi med en strek på skalaen nedenfor **i hvilken grad** du opplever ditt stemmeproblem.

Ingen plager ____ **Uutholdelige plager**

5. Hvor **ofte** opplever du stemmeproblemene?
   - ☐ hver dag
   - ☐ ukentlig
   - ☐ annenhver uke
   - ☐ en gang i måneden
   - ☐ annenhver måned
   - ☐ et par ganger i året

6. Hvor mye bruker du din stemme på **jobb**?
   - ☐ jobber ikke
   - ☐ nesten ingenting (snakket lite)
   - ☐ noe (eks. kontor, mye data osv.)
   - ☐ normalt (eks. samtale med kollegaer, noen telefoner osv.)
   - ☐ mye (eks. en del telefoner, møtevirksomhet, noe undervisning osv.)
   - ☐ svært mye (eks. undervisning, foredrag, telefoner osv.)

7. Hvor mye bruker du din stemme i **fritiden**?
   - ☐ nesten ingenting (snakket lite i sosiale sammenhenger)
   - ☐ noe (når jeg måtte, når jeg var ute og handlet og lign.)
   - ☐ normalt (snakket med familie og venner)
   - ☐ mye (likte å prate/være sosial, interesser som krevde stemmebruk)
   - ☐ svært mye (sang i kor eller lignende aktiviteter)

8. Hvilke **tiltak/behandling** er satt inn for å bedre stemmevanskene?

- ☐ Ingen
- ☐ Kirurgisk inngrep/operasjon
- ☐ Logoped behandling
- ☐ Kirurgi og logoped

9. Hvilke tiltak har **du** gjort for å bedre din stemme (sett mer enn ett kryss om nødvendig)?

- ☐ Ikke gjort noe
- ☐ Har skiftet yrke/måtte endre arbeidsoppgaver på grunn av stemmen
- ☐ Redusert egen stemmebruk
- ☐ Unngår å bruke stemmen
- ☐ Gjør ofte ”stemmeøvelser”
- ☐ Er bevist på hvordan jeg bruker stemmen

Annet: ________________________

10. Hva **føler du** har gitt størst bedring på stemmen din?

- ☐ Ingenting
- ☐ Kirurgi/operasjon
- ☐ Logopedisk behandling
- ☐ Kirurgi og logoped
- ☐ Egen innsats

Annet: ___________________

11. Røyking? (Det er veldig viktig at du svarer så korrekt som mulig. Om du aldri har røykt, så svarer du ikke her.

- Antall sigaretter pr dag **nå**: ____
- Antall sigaretter pr. dag **før** (om du har redusert/sluttet):______
- Antall **år** du har røykt, totalt: _____
- Hvis du har sluttet å røyke, i så fall hvilket år? _____

12. Hvilket yrke har du/har du hatt før:____________________________________

13. Driver du med stemmekrevende hobby? Hva:___________________________
____

14. Kryss av ved de plagene i skjemaet under som eventuelt gjelder for deg **nå**.

Slim i halsen:

- ☐ ingen plager
- ☐ litt plaget
- ☐ plaget
- ☐ meget plaget
- ☐ uutholdelig plaget

Tørrhet i halsen:

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- ☐ litt plaget
- ☐ plaget
- ☐ meget plaget
- ☐ uutholdelig plaget

Tretthet i halsen:

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- ☐ plaget
- ☐ meget plaget
- ☐ uutholdelig plaget

Kremting:

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- ☐ litt plaget
- ☐ plaget
- ☐ meget plaget
- ☐ uutholdelig plaget

Smerter i halsen:

- ☐ ingen plager
- ☐ litt plaget
- ☐ plaget
- ☐ meget plaget
- ☐ uutholdelig plaget

Heshet:

- ☐ ingen plager
- ☐ litt plaget
- ☐ hes stemme
- ☐ meget hes
- ☐ uutholdelig plaget med hes stemme

TAKK FOR HJELPEN

VOICE HANDICAP INDEX (VHI)

Instruksjon: Dette er utsagn som mange personer har brukt for å beskrive stemmen sin og hvilken innvirkning den har på livet deres. Sett ring rundt svaret som viser hvor ofte du har den samme erfaringen.

	Aldri	Nesten aldri	Noen ganger	Nesten alltid	Alltid
1. Stemmen min gjør at det er vanskelig for folk å høre meg.	0	1	2	3	4
2. Jeg går tom for luft når jeg snakker.	0	1	2	3	4
3. Folk har vanskelig for å forstå meg i et rom med støy.	0	1	2	3	4
4. Stemmen min varierer i løpet av dagen.	0	1	2	3	4
5. Familien min har problemer med å høre meg når jeg roper på dem fra forskjellige steder i huset.	0	1	2	3	4
6. Jeg bruker telefonen sjeldnere enn jeg har behov for.	0	1	2	3	4
7. På grunn av stemmen er jeg anspent når jeg snakker.	0	1	2	3	4
8. Jeg har lett for å unngå grupper av mennesker p.g.a stemmen min.	0	1	2	3	4
9. Det synes som om folk irriterer seg over stemmen min.	0	1	2	3	4
10. Folk spør: "Hva er i veien med stemmen din ?"	0	1	2	3	4
11. Jeg snakker mindre med venner, naboer eller slektninger p.g.a. stemmen min.	0	1	2	3	4
12. Folk ber meg gjenta det jeg sier når jeg snakker med dem ansikt til ansikt.	0	1	2	3	4
13. Stemmen min høres sprukken og tørr ut.	0	1	2	3	4

	Aldri	Nesten aldri	Noen ganger	Nesten alltid	Alltid
14. Jeg føler at jeg må presse stemmen for å lage lyd.	0	1	2	3	4
15. Folk har liten forståelse for stemmeproblemene mine.	0	1	2	3	4
16. Stemmevanskene mine begrenser privat og sosialt liv.	0	1	2	3	4
17. Klarheten i stemmen min er vanskelig å forutsi.	0	1	2	3	4
18. Jeg prøver å forandre stemmen min for å høre annerledes ut.	0	1	2	3	4
19. Jeg føler jeg blir holdt utenfor i samtaler p.g.a. stemmen min.	0	1	2	3	4
20. Jeg anstrenger meg ganske mye for å snakke.	0	1	2	3	4
21. Stemmen min er verre om kvelden.	0	1	2	3	4
22. Stemmeproblemene mine er årsak til at jeg mister inntekt.	0	1	2	3	4
23. Jeg blir stresset av stemmen min.	0	1	2	3	4
24. Jeg går mindre ut p.g.a. stemmeproblemene mine.	0	1	2	3	4
25. Stemmen min får meg til å føle meg handikappet.	0	1	2	3	4
26. Stemmen min svikter midt i en samtale.	0	1	2	3	4
27. Jeg blir irritert når folk ber meg om å gjenta.	0	1	2	3	4
28. Jeg føler meg flau når folk ber meg om å gjenta.	0	1	2	3	4
29. Stemmen min får meg til å føle meg utilstrekkelig.	0	1	2	3	4
30. Jeg skammer meg over stemmeproblemene mine.	0	1	2	3	4

EORTC QLQ-C30 (versjon 3.0)

Vi er interessert i forhold vedrørende deg og din helse. Vær så vennlig å besvar hvert spørsmål ved å sette en ring rundt det tallet som best beskriver din tilstand. Det er ingen 'riktige' eller 'gale' svar. Alle opplysninger vil bli behandlet konfidensielt.

	Ikke i det hele tatt	Litt	En del	Svært mye
1. Har du vanskeligheter med å utføre anstrengende aktiviteter, slik som å bære en tung handlekurv eller en koffert?	1	2	3	4
2. Har du vanskeligheter med å gå en lang tur?	1	2	3	4
3. Har du vanskeligheter med å gå en kort tur utendørs?	1	2	3	4
4. Er du nødt til å ligge til sengs eller sitte i en stol i løpet av dagen?	1	2	3	4
5. Trenger du hjelp til å spise, kle på deg, vaske deg eller gå på toalettet?	1	2	3	4

I løpet av den siste uka:	Ikke i det hele tatt	Litt	En del	Svært mye
6. Har du hatt redusert evne til å arbeide eller utføre andre daglige aktiviteter?	1	2	3	4
7. Har du hatt redusert evne til å utføre dine hobbyer eller andre fritidsaktiviteter?	1	2	3	4
8. Har du vært tungpusten?	1	2	3	4
9. Har du hatt smerter?	1	2	3	4
10. Har du hatt behov for å hvile?	1	2	3	4
11. Har du hatt søvnproblemer?	1	2	3	4
12. Har du følt deg slapp?	1	2	3	4
13. Har du hatt dårlig matlyst?	1	2	3	4
14. Har du vært kvalm?	1	2	3	4
15. Har du kastet opp?	1	2	3	4

16. Har du hatt treg mage?	1	2	3	4
17. Har du hatt løs mage?	1	2	3	4
18. Har du følt deg trett?	1	2	3	4
19. Har smerter påvirket dine daglige aktiviteter?	1	2	3	4
20. Har du hatt problemer med å konsentrere deg, f.eks med å lese en avis eller se på TV?	1	2	3	4
21. Har du følt deg anspent?	1	2	3	4
22. Har du vært engstelig?	1	2	3	4
23. Har du følt deg irritabel?	1	2	3	4
24. Har du følt deg deprimert?	1	2	3	4
25. Har du hatt problemer med å huske ting?	1	2	3	4
26. Har din fysiske tilstand eller medisinske behandling påvirket ditt familieliv?	1	2	3	4
27. Har din fysiske tilstand eller medisinske behandling påvirket dine sosiale aktiviteter?	1	2	3	4
28. Har din fysiske tilstand eller medisinske behandling gitt deg økonomiske problemer?	1	2	3	4

Som svar på de neste spørsmålene sett en ring rundt det tallet fra 1 til 7 som best beskriver din tilstand

29. Hvordan har din helse vært i løpet av den siste uka?

1	2	3	4	5	6	7
Svært dårlig						Helt utmerket

30. Hvordan har livskvaliteten din vært i løpet av den siste uka?

1	2	3	4	5	6	7
Svært dårlig						Helt utmerket

EORTC QLQ - H&N35

En del pasienter opplever av og til at de har noen av de følgende symptomer eller problemer. Vær vennlig å angi i hvilken grad du har hatt disse symptomene eller problemene i løpet av den siste uka. Sett en ring rundt det tallet som best beskriver din tilstand.

I løpet av den siste uka:	Ikke i det hele tatt	Litt	En del	Svært mye
31. Har du hatt smerter i munnen?	1	2	3	4
32. Har du hatt smerter i kjeven?	1	2	3	4
33. Har du hatt smerter i halsen?	1	2	3	4
34. Har du hatt noe i vrangstrupen når du har svelget?	1	2	3	4
35. Har du hatt problemer med tennene?	1	2	3	4
36. Har du hatt problemer med å gape høyt?	1	2	3	4
37. Har du vært tørr i munnen?	1	2	3	4
38. Har du hatt seigt spytt?	1	2	3	4
39. Har du hostet?	1	2	3	4
40. Har du vært hes?	1	2	3	4
41. Har du følt deg syk?	1	2	3	4
42. Har du hatt vanskeligheter med å spise?	1	2	3	4
43. Har du hatt vanskeligheter med å snakke med andre mennesker?	1	2	3	4
44. Har du hatt vanskeligheter med å snakke i telefonen?	1	2	3	4
45. Har du hatt vanskeligheter med å ha sosial omgang med familien?	1	2	3	4
46. Har du hatt vanskeligheter med å ha sosial omgang med venner?	1	2	3	4
47. Har du hatt vanskeligheter med å være ute på offentlige steder?	1	2	3	4

I løpet av den siste uka:	**Nei**	**Ja**
48. Har du brukt smertestillende?	1	

”Eysenck” (EPI)

INSTRUKSJON

Dette er noen spørsmål om hvordan du vanligvis opptrer, føler og handler. På hvert av spørsmålene skal du enten svare ‘ja’ eller ‘nei’ ved å sette en ring rundt det svaret som passer best for deg. Svar så raskt som mulig, men avgi det svaret som er mest dekkende for din vanlige måte å være på.

Det skal bare ta noen minutter å fylle ut spørreskjemaet. Pass på at du ikke hopper over noen av spørsmålene.

Dette er ingen evneprøve og derfor er ingen svar riktig eller gale.

1. Lengter du ofte etter spenning?	JA	NEI
2. Har du ofte behov for forståelsesfulle venner som kan muntre deg opp?	JA	NEI
3. Er du vanligvis uten bekymringer?	JA	NEI
4. Er det vanskelig for deg å godta ‘nei’ som et svar?	JA	NEI
5. Stopper du opp og tenker over tingene før du utfører dem?	JA	NEI
6. Holder du alltid et løfte, uansett hvor besværlig det er for deg å gjennomføre det?	JA	NEI
7. Har du et vekslende humør?	JA	NEI
8. Er det vanligvis slik at du sier og gjør ting raskt uten å tenke?	JA	NEI
9. Føler du deg noen ganger nedfor uten god grunn?	JA	NEI
10. Ville du gjøre nesten hva som helst, hvis noen utfordrer deg?	JA	NEI
11. Kan du plutselig føle deg sjenert når du ønsker å snakke til en fremmed som du synes er tiltrekkende?	JA	NEI
12. Mister du en gang i blant beherskelsen og blir sint?	JA	NEI
13. Handler du ofte på et øyeblikks innskytelse?	JA	NEI

14. Bekymrer du deg ofte over ting du ikke skulle ha sagt eller gjort? JA NEI

15. Ville du heller lese om mennesker enn å møte dem? JA NEI

16. Blir dine følelser lett såret? JA NEI

17. Liker du å gå mye ut? JA NEI

18. Har du av og til tanker og ideer som du ikke ville like at andre kjente til? JA NEI

19. Bobler du noen gang over av energi, og er du andre ganger uten tiltakslyst? JA NEI

20. Foretrekker du å ha få, men utvalgte venner? JA NEI

21. Dagdrømmer du mye? JA NEI

22. Når folk bruker kjeft på deg, kjefter du da tilbake? JA NEI

23. Plages du ofte av skyldfølelse? JA NEI

24. Har du bare gode vaner? JA NEI

25. Kan du vanligvis slå deg løs og ha det morsomt i et livlig selskap? JA NEI

26. Betrakter du deg selv som meget stiv og anspent? JA NEI

27. Synes andre mennesker at du er svært livlig? JA NEI

28. Når du har utført noe viktig, er det da ofte slik at du etterpå synes du kunne ha gjort det bedre? JA NEI

29. Er du stort sett stille og tilbakeholden når du er sammen med andre? JA NEI

30. Hender det at du driver med sladder? JA NEI

31. Har du ofte så mange tanker og ideer at du ikke får sove? JA NEI

32. Hvis det er noe du ønsker å få vite, ville du heller slå opp i en bok fremfor å spørre om det? JA NEI

33. Får du noen gang hjertebank? JA NEI

34. Liker du arbeid som krever intens konsentrasjon? JA NEI

35. Får du anfall hvor du rister eller skjelver? JA NEI

36. Ville du oppgi alt til tollen selv om du visste at du aldri ville bli oppdaget? JA NEI

37. Misliker du å være sammen med mennesker som alltid driver gjøn med hverandre? JA NEI

38. Blir du lett irritert? JA NEI

39. Liker du å gjøre ting som krever at du må handle raskt? JA NEI

40. Bekymrer du deg for at fryktelige ting skal skje? JA NEI

41. Beveger du deg sent uten hastverk? JA NEI

42. Har du noen gang kommet for sent på arbeid eller til en avtale? JA NEI

43. Har du ofte mareritt om natten? JA NEI

44. Liker du så godt å snakke med noen at du aldri går glipp av en anledning til å snakke med fremmede? JA NEI

45. Plages du av verking og smerter i kroppen? JA NEI

46. Ville du bli meget ulykkelig dersom du ikke det meste av tiden hadde mange mennesker rundt deg? JA NEI

47. Betrakter du deg selv som en nervøs person? JA NEI

48. Kjenner du noen mennesker som du absolutt ikke liker? JA NEI

49. Betrakter du deg selv som temmelig selvsikker? JA NEI

50. Blir du lett såret dersom andre finner feil med deg eller ditt arbeid? JA NEI

51. Har du vanskelig for riktig å more det i et livlig selskap? JA NEI

52. Er du plaget av mindreverdighetsfølelse? JA NEI

53. Greier du vanligvis å skape liv i et heller kjedelig selskap? JA NEI

54. Hender det noen ganger at du snakker om ting du ikke har greie på? JA NEI

55. Bekymrer du deg for din helse? JA NEI

56. Liker du å spille andre et puss? JA NEI

57. Plages du av søvnløshet? JA NEI

Table 1 Translations of VHI

Author(s) (Language) Year	Objectives	Material and methods	Results
Jacobson et al. (Original English) 1997	Develop self -assessment measures and compare with VHI	An initial pool of 85 items was developed empirically from case history interviews, reduced to a 30-item final version, administered to 63 consecutive patients on two occasions in an attempt to assess test-retest stability.	A Pearson product-moment correlation coefficient was used to compare subjects' VHI scores and judgments of severity. Results indicated a moderate relationship between the two patient self-assessment measures ($r = 0.60$).
Nawka et al. (German) 2003	Investigate the validity of VHI as diagnostic tool in German.-speaking countries.	Adult patients (316), 221 female and 95 male. A factor analysis in order to structure the items yields four factors that can be interpreted as negative voice experience.	The mean VHI scores differ significantly from each other in different degrees of voice disturbance. The voice handicap index is qualified as a diagnostic tool for German-speaking countries.
Guimarares & Abberton (Portugese) 2004	Investigate the validity of VHI as diagnostic tool in Portugese language.	The subjects were 49 patients and 56 controls. Repeated-measures analysis ANOVA carried out with group (dysphonics and controls).	Subjects with an ENT diagnosis of functional disorders, tissue changes, and mass lesions show higher VHI scores than the healthy and minor abnormalities.
Woisard et al. (French) 2004	To investigate the VHI test-retest reliability and the internal consistency reliability.	Normal subjects (52) and patients (63) with voice disorders. Replied to the questionnaire at the day of their first consultation and 10 to 30 days after the consultation (before any treatment).	Test-Retest stability of the pathological subjects was found to be satisfactory for both total score and subscale scores. Difference scores were derived for the VHI total score, for the physical subscale and for the functional and emotional.subscales

Amir et al. (Hebrew) 2005	To use VHI for assessing validity and reliability and evaluate group differences	Parallel group design. 182 patients with various laryngeal pathologies and a control group of 171 people.	Control group obtained significantly lower scores on the overall VHI score, as well as on all three subscale scores.
Hakkesteegt et al. (Dutch) 2006	Investigate the validity of VHI as diagnostic tool in Dutch language	Test-retest study. A group of 104 patients (56 male, 48 female) with voice complaints completed the VHI twice with a mean interval of 13 days.	There was a good correlation between the first and the second measurement. They found that a 14-point difference in total score of the Dutch VHI for one patient at two points in time is significant.
Núñez-Batalla et al. (Spanish) 2007	To perform a prospective instrument validation of VHI	Including 232 dysphonic patients and 38 non-dysphonic individuals. .	High test-retest reliability and high item-total correlation for both Spanish VHI-30 and VHI-10. Internal consistency demonstrated. A significant correlation was found between the VHI scores and the patients' self-rated dysphonic severity.
Kiliç et al. (Turkish) 2008	Translation of VHI to Turkish and test reliability and validity.	VHI was translated to Turkish by 10 otolaryngologists, then it was translated back to English by a linguist, and the final text was prepared by the evaluation committee composed of three members. Administered to a group of 220 subjects twice.	Internal consistency reliability was found to be highly significant The factor analysis yielded three factors explaining 64.8% of the total variance. The corrected item-total correlation coefficients ranged from 0.50 to 0.80.

Schindler et al. (Italian) 2009	To assess the correlation between VHI scores and the grade of voice disorder and gender.	Cross-sectional survey study. 175 patients with voice disorders, 4 groups and 84 controls. The test-retest reliability was assessed through the Pearson correlation test. Pathological group were compared with controls through the Kruskal-Wallis test.	The control group scored significantly lower than the four groups of voice-disordered patients. The overall VHI score positively correlated with the grade of voice disorder. In the voice-disorder group, age and gender were not correlated to the overall VHI score and to their three domains.
Švec et al. (Czech) 2009	To develop an official, linguistically corrected Czech version of VHI.	This study takes three independent translations of VHI and unifies them into an official, linguistically corrected Czech version.	The VHI score can be used for verifying the successfulness of treatment methods in voice disorders.
Ohlsson & Dotevall (Swedish) 2009	To investigate whether Sw-VHI distinguish between dysphonic subjects and controls.	Fifty-seven adult, dysphonic patients and 15 healthy controls.They rated the degree of vocal fatigue and hoarseness on visual analogue scales. A perceptual voice evaluation was also performed. Test-retest reliability was analyzed in 38 subjects without voice complaints.	Sw-VHI distinguished between dysphonic subjects and controls (PB0.001). Cronbach's alpha 0.84 and test-retest reliability. The data indicate that a difference above 13 points for the total Sw-VHI score is significant for an individual when comparing two different occasions.
Behlau et al. (Brazilian Portuguese) 2009	To evaluate VHI validity, reliability, reproducibility/ responsiveness	The translated version was completed by 52 individuals with vocal complaints and by a control group of 64 subjects. All participants also completed a self-rating vocal quality scale.	A positive correlation was found between the VHI and the self-rating vocal quality scale. The subjects in the control group had lower scores compared with the subjects with voice disorders for the overall VHI score and for the three domains.
Xu et al. (Mandarin Chinese) 2009		Dysphonic patients (1766) and 120 control subjects. Two-hundred and ten of the patients were treated with phonosurgery or BOTOX injection.	The test-retest reliability was shown. Correlations between the subscales and the overall VHI as well as among the subscales were all significant. Treatment leads to statistically improvement in VHI scores

Helidoni et al. (Greek) 2010	VHI was translated into Greek with cultural adaptations to accommodate certain words	Subjects (67) with various voice disorders and a control group (79). Also a self-rating scale regarding the severity of their voice disorder.	A moderate correlation was found between the VHI and the self-rating severity scale. The subjects in the control group had lower scores compared to the subjects with voice disorders for the overall VHI score and for the three domains.
Saleem & Natour (Arabic) 2010	To test internal consistency reliability and validity of VHI	Participants (77 females and 35 males). Assigned to seven pathological groups.	Results showed high internal consistency. Test-retest reliability was found to be strong. Validity results indicated moderate correlations between total VHI score and responses to severity.
Datta et al. (Hindi) 2011	To test internal consistency reliability and validity of VHI	Patients (175) controls (84). 63 randomly selected patients filled VHI twice for test-retest. Comparison between the two groups and with self-perceived grade of voice problem.	High internal consistenscy was found. The dysphonic scored significant lower than controls. Total VHI score correlated positively with patients self-perceived grade of voice problem.
Taguchi et al. (Japanese) 2012	To compare VHI scores between patients with voice disorders	VHI assessment was done before and after treatment in 161 of patients (63 males and 98 females).	In most diseases, functional and physiological scores were higher than emotional scores. In any treated patients, those with vocal nodule, vocal polyp, polypoid vocal fold, and recurrent laryngeal nerve paralysis, VHI scores decreased after therapeutic intervention.
Karlsen et al. (Norwegian) 2012	To test internal consistency and validity of VHI	Following standard translation, 126 healthy subjects and 126 patients with laryngeal disease answered the Norwegian translation of the VHI-30.	The VHI-30(N) showed a high Cronbach alpha. Differences between patient and control groups were significant for all questions on the VHI-30(N). A cutoff score at 19 included approximately 95% of the patients and 10% of the controls.

Bonetti & Bonetti (Croatin) 2012	To test internal consistency and validity of VHI	Thirty-eight subjects with voice disorders and 30 subjects without voice complaints. Auditory perceived grade of dysphonia.	Internal consistency was shown. Subjects with voice disorders had significantly higher average total VHI score and scores in each of the three VHI domains (functional, physical, and emotional). The overall VHI score positively correlated with auditory perceived grade of dysphonia.
Moradi et al. (Persian) 2013	To study the reliability and validity	The subjects were 80 patients with voice disorders and 80 as a control group. All subjects filled in the Persian version of VHI. The test was repeated 2 weeks later.	All items had significant discrimination coefficient. The internal consistency and reliability of test and retest in VHI total score and three subtests were achieved.
Trinite & Sokolovs (Latvian) 2014	To study the test-retest stability, internal consistency of the Lat-VHI, and content and convergent validity of the Latvian version of the VHI.	Parallel group design. The VHI was translated and adapted to Latvian. The translated version of the VHI (Lat-VHI) was completed by 54 patients and 73 controls. A test-retest group included 54 subjects without voice Problems.	Test-retest reliability was found. High internal consistency was observed. The Pearson moment correlation coefficient indicates a high correlation among total scale and subscales as well as a high correlation among subscales in the patient group. Convergent validity was discovered in the patient group.

Original papers I - IV

III

Health-related Quality of Life as Studied by EORTC QLQ and Voice Handicap Index Among Various Patients With Laryngeal Disease

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Summary: Objectives. Patients with voice-related disorders are often treated by a multidisciplinary team including assessment by patient-reported outcome measures. The present paper aims at documenting the importance of including general health-related quality of life (HRQoL) measures to clinical investigations.

Study design. The participants (N = 80 larynx cancer, N = 32 recurrent palsy, N = 23 dysfunctional, N = 75 degenerative/inflammation, N = 19 various) were included consecutively at the laryngology clinic at Haukeland University Hospital. In addition, HRQoL data were included from one national group with laryngectomies (N = 105), one group with various patients formerly treated for head and neck squamous cell carcinoma (N = 96), and one population-based reference group (N = 1956).

Method. Obtained were the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ), the Voice Handicap Index (VHI), and the Eysenck Personality Inventory (EPI) neuroticism scores.

Results. By analysis of variance, we have determined significant dependence of groups analyzing the sum global QoL/health index (F = 9.47; $P < 0.001$), the functional HRQoL sum score ($F_{5,2373} = 7.14$, $P < 0.001$), and the symptom sum HRQoL scores ($F_{7,2381} = 8.13$; $P < 0.001$). In particular, patients with recurrent palsy and laryngeal cancer had lowered HRQoL. At the index levels, in particular dyspnea scores, were scored depending on larynx disease group ($F_{7,2288} = 24.4$; $P < 0.001$). The VHI score correlated with the EORTC H&N35 "speech" index with a common variance of 52%. VHI scores correlated with level of neuroticism with 8% common variance ($P < 0.001$) and EORTC scores with 22% ($P < 0.001$).

Conclusion. In particular, among patients with voice-related disease, those with recurrent palsy and laryngeal cancer had lower HRQoL. Furthermore, the HRQoL and VHI scores were inversely tied to neuroticism.

Key Words: EORTC QLQ–Voice Handicap Index–Norwegian–voice disorders–quality of life.

INTRODUCTION

Patients with voice-related disorders are often examined and treated by a team including an ear, nose, and throat specialist and a speech therapist. This requires registering clinical and patient-reported information as reliable and valid as possible. The European Laryngological Society has proposed a basis protocol for assessment of voice-related diseases,[1] which includes assessment by patient-reported outcome measures. Aims of this protocol include allowing comparison of treatments of voice-related diseases across cultures, as well as assessing impact of voice disorders in the health-related quality of life (HRQoL). This *may* include both general and symptom-specific HRQoL items.[2] The understanding of HRQoL among patients with larynx disease is, however, limited and should therefore be of high interest to investigate.

The European Organization for Research and Treatment of Cancer (EORTC) has developed a line of HRQoL questionnaires aimed at cancer patients.[3] These HRQoL questionnaires consist of one questionnaire developed as a general HRQoL questionnaire,[3] as well as many site-specific questionnaires.[4] The EORTC Core Quality of Life Questionnaire (QLQ)-C30 general questionnaire consists of nine multi-item scales, five functional scales, three symptom scales, one global health scale, and one global HRQoL scale. Several single-item symptom measures are also included. Although developed with an aim at evaluating the HRQoL of cancer patients, this questionnaire has also been suggested to be used to assess HRQoL in general.[5,6] Norwegian population norms are also available.[7,8] As patients with larynx disease include cancer patients, this questionnaire may be useful among mixed patients with larynx disease. An aim of this investigation is thus to study the EORTC QoL questionnaire yield among patients with larynx disease.

Several patient-reported outcome measures aimed at measuring the specific impact of voice-related diseases on activities of daily life have been developed.[9] The Voice Handicap Index (VHI) constitutes one such example and includes questions measuring various perceived consequences of voice disease. The Agency for Healthcare Research and Quality reported in 2002 that the VHI met stringent criteria for reliability, validity, and availability of normative data.[10] The VHI has been translated into many different languages. Verdonck-de Leeuw et al[11] have validated the VHI by assessing equivalence of European translations of the questionnaire to the following languages: German, French, Dutch, Italian, Portuguese, Belgian, and Swedish.[11] A Norwegian translation has also recently been published.[12] Several investigators have furthermore used VHI scores to study effects

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of larynx disease treatment.[13–15] The VHI may be viewed as a voice-specific HRQoL instrument.[16] One present aim was to study the relation between the VHI score and the various EORTC QLQ scores.

Studies investigating HRQoL in relation to psychosocial conditions among patients are an emerging interest in medicine, and such research show that especially personality is associated to HRQoL scores more closely than disease-derived factors.[17–19] To study this further among patients with larynx disease has also been an aim of the present investigation.

The aims of this study were to investigate HRQoL among patients with voice disease and to study the relation between HRQoL and present neuroticism.

MATERIALS AND METHODS

Participants

This study consists of four cohorts:

I: Cohort of Haukeland University Hospital (HUH) patients with voice disease

The participants (N = 229) consisted of 138 men (median age 61, range 24–86) and 91 women (median age 51, range 18–79) and were included consecutively following appointments at the laryngology clinic at HUH. The clinic receives patients referred both from family physicians and from surrounding private practice ear, nose, and throat specialists. The patients received the questionnaires in an envelope at the consultation and returned the questionnaires by mail after filling out answers at home. The return rate of the questionnaires was 81%. The characteristics of these patients are given in Table 1.

II: General Norwegian reference

A randomly selected sample of 3000 people, reflecting the age and gender distribution of the adult Norwegian population, was obtained by a random draw from the adult Norwegian population. Of the 3000 invited, 1956 returned the questionnaire and were available for analyses. The EORTC QLQ-C30 (version 2.0) and a questionnaire about demographic data and health were mailed. Detailed information about these reference HRQoL data has been published previously.[7,8]

III: Cohort of patients from HUH formerly treated for head and neck squamous cell carcinoma (HNSCC)

This group included 96 successfully treated patients with HNSCC from western Norway aged less than 80 years who were primarily treated at HUH. HRQoL data were collected a median of 4 years after the primary diagnosis of HNSCC. The patients with HNSCC responded to the questionnaires by structured interviews. The patient, tumor, and therapy characteristics have been published previously.[3]

IV: Cohort of National Norwegian Laryngectomies (NLS)

All patients with laryngectomy in Norway become members of the NLS, a subsidiary of the Norwegian Cancer Society. Copies of EORTC QLQ-C30 (version 3.0) were mailed to all registered members of the NLS below 80 years of age. A second invitation was mailed if the patients did not respond to the first. In total, 104 patients answered the questionnaires, and the specific data have been published previously.[20] The vast majority of these patients were laryngectomized owing to cancer of the larynx.

Cohort I diagnostic workup

The patients were subjected to standard medical and voice therapist examination according to the standard procedure suggested by the European Laryngological Society.[1] The diagnostic groups were set according to previously published flowcharts[21] (Table 1).

TABLE 1.
Number of Voice Patients Included, Age, Sex, Voice Use, Reported Degree of Voice Problems, Smoking, and Group Allocation, by Diagnosis (n = 229)

	Number		Age		Voice Use		Voice Problem		Smoking	
	Total	Female	Median	Range	Median %	Range %	Degree 0–1	Degree 2–3	Number	Group Allocation
Cancer	80	7	67	37–85	45	18–91	59	15	70	Cancer
Recurrent palsy	32	16	59	34–79	64	27–91	13	19	19	Recurrent palsy
Dysfunctional	23	15	55	29–77	82	18–100	12	11	6	Dysfunctional
Reinke edema	16	12	54	42–69	73	36–100	9	7	15	Degen./Inflam.
Laryngitis	16	9	73	40–86	55	27–91	10	6	9	Degen./Inflam.
Polyp	17	7	46	25–62	82	45–91	6	11	11	Degen./Inflam.
Cyst	12	6	50	20–71	68	9–91	8	3	4	Degen./Inflam.
Papilloma	8	3	39	21–54	77	64–82	4	4	2	Degen./Inflam.
Dysplasia	6	2	63	54–72	73	36–100	5	1	5	Degen./Inflam.
Other	12	8	58	21–81	45	36–100	6	6	8	Others
Nodules	6	5	29	18–43	100	55–100	1	4	1	Dysfunctional
Aphonia	1	0	56	56	57	57	0	1	0	Others
Total	229	90	59	21–86	64	9–100	133	88	150	

The VHI

Members of cohort I answered the VHI. The VHI includes 30 statements (items).[22] The patients answer on a 5-point Likert-type scale (from 0 = never to 4 = always). The total VHI sum score ranges from 0 to 120 points. The highest value represents maximum level of self-experienced voice handicap. The questionnaire has been translated into Norwegian.[12]

EORTC QLQ HRQoL measure

The general HRQoL of the patients was assessed using the EORTC QLQ-C30 questionnaire.[3] The QLQ-C30 contains a global health scale, five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain and nausea/vomiting), and six single items (dyspnea, insomnia, anorexia, constipation, diarrhea, and financial difficulties). To the members of cohort I, some indexes from the EORTC QLQ-H&N35 questionnaire were also included (speech, teeth problems, opening mouth, dry mouth, sticky saliva, coughing, and feeling ill).[23] The answers were given according to a 4-point Likert format, with the exception of questions about general health and quality of life, which are given according to a 7-point Likert format. All responses were scored in accordance with the EORTC Scoring Manual. The C30 functional scales and the global scale were transformed so that 100% indicates best function and 0% indicates least function on the individual QoL index, whereas the C30 symptom and H&N35 scales were transformed so that 0% indicates the lowest and 100% indicates the most serious symptoms. The Cronbach alpha values of the sum scores of functional indexes ($\alpha = 0.85$) and symptoms indexes ($\alpha = 0.82$) were satisfactory.

Additional questionnaires used

Cohort I answered in addition questions about background information regarding occupation, a 4-point Likert scale stating how seriously the voice disease was experienced, and a 7-point Likert scale about level of voice use (1 = quiet listener; 7 = extremely talkative) at home and at work.

Statistics

We used a commercially available statistical program package (*SPSS Statistics* 22.0, IBM, Armonk, NY, USA) for statistical analysis. Statistical significance was considered if $P < 0.05$. All P values reported represent two-sided tests. Cronbach alpha, Pearson correlation, partial correlation, and multivariate analysis of variance (MANOVA) analyses followed by *post hoc* Bonferroni method were calculated as indicated.

RESULTS

HRQoL related to diagnoses (all cohorts)

We have determined significant dependence of disease group analyzing the sum global QoL/health index ($F_{7,2362} = 9.47$; $P < 0.001$) (Figure 1). *Post hoc* analyses showed that the reference population scored higher than the patients with recurrent palsy and ($P < 0.001$) and the patients with degenerative or inflammatory disease ($P = 0.002$). Furthermore, patients with recurrent palsy scored lower than the patients formerly treated for HNSCC and the laryngectomized patients. Finally, patients with degenerative/inflammatory disease scored lower than the patients formerly treated for HNSCC.

When analyzed using functional HRQoL sum score as depending factor, a significant effect of group allocation ($F_{7,2373} = 7.14$, $P < 0.001$) was determined (Figure 1). *Post hoc* analyses showed that the laryngectomized patients ($P < 0.001$) and the patients with recurrent palsy ($P < 0.05$) scored lower than the reference population.

The emotional index was scored depending on group ($F_{7,2210} = 4.57$; $P < 0.001$) (Figure 2). The only significant difference was that the mean of the reference population was higher than the mean of the laryngectomized group. The cognitive index was also scored depending on group ($F_{7,2210} = 2.74$; $P < 0.01$), but no particular group difference was observed following *post hoc* analysis.

The physical index was also scored depending on group allocation ($F_{7,2210} = 12.19$; $P < 0.001$) (Figure 2). *Post hoc* analyses showed that the reference population scores were higher than those of the laryngectomized patients ($P < 0.001$), patients with HNSCC, and the patients with laryngeal cancer ($P < 0.05$). In addition, patients with degenerative/inflammatory disease scored higher than the laryngectomized group. The social index was also scored depending on group allocation ($F_{7,2210} = 13.6$; $P < 0.001$) (Figure 1). *Post hoc* analyses showed that the reference population scored higher than all the specific patient groups ($P < 0.05$–0.001), except the general HNSCC group. Furthermore, the recurrent palsy group scored lower than the general HNSCC group ($P < 0.05$). The role index was also scored depending on group ($F_{7,2210} = 4.69$; $P < 0.001$). *Post hoc* analyses showed that the scores of patients with recurrent palsy were lower than the scores of the reference population ($P < 0.001$).

ANOVA analyses with the symptom sum HRQoL scores showed a significant effect depending on group allocation ($F_{7,2381} = 8.13$; $P < 0.001$) (Figure 1). *Post hoc* analyses showed that scores of the reference population were significantly lower than that of the laryngectomized group ($P < 0.001$) and recurrent palsy group ($P < 0.05$). In addition, the laryngectomized patients scored lower than the patients with general HNSCC and patients with degenerative/inflammatory larynx disease (both $P < 0.05$).

At the EORTC C30 index levels, in particular dyspnea, scores were scored depending on disease group ($F_{7,2288} = 24.4$; $P < 0.001$) (Figure 3). All patient groups, except those formerly treated for HNSCC and the dysfunctional group, scored with more symptoms than the reference population ($P < 0.001$). In addition, the laryngectomized patients ($P < 0.001$) and those with recurrent palsy ($P < 0.05$) scored with more symptoms than the group of patients formerly treated for HNSCC ($P < 0.001$). Level of financial strain was also scored depending on disease group ($F_{7,2288} = 7.6$; $P < 0.001$). In particular, the laryngectomized patients ($P < 0.001$) and those with recurrent nerve palsy ($P < 0.05$) reported more financial strain than the reference population.

MANOVA analyses when including the “dyspnea” indexed as covariate removed the dependence of “diagnostic group” from the functional and symptom sum score results, but not from the global QoL/health sum score results (results not shown).

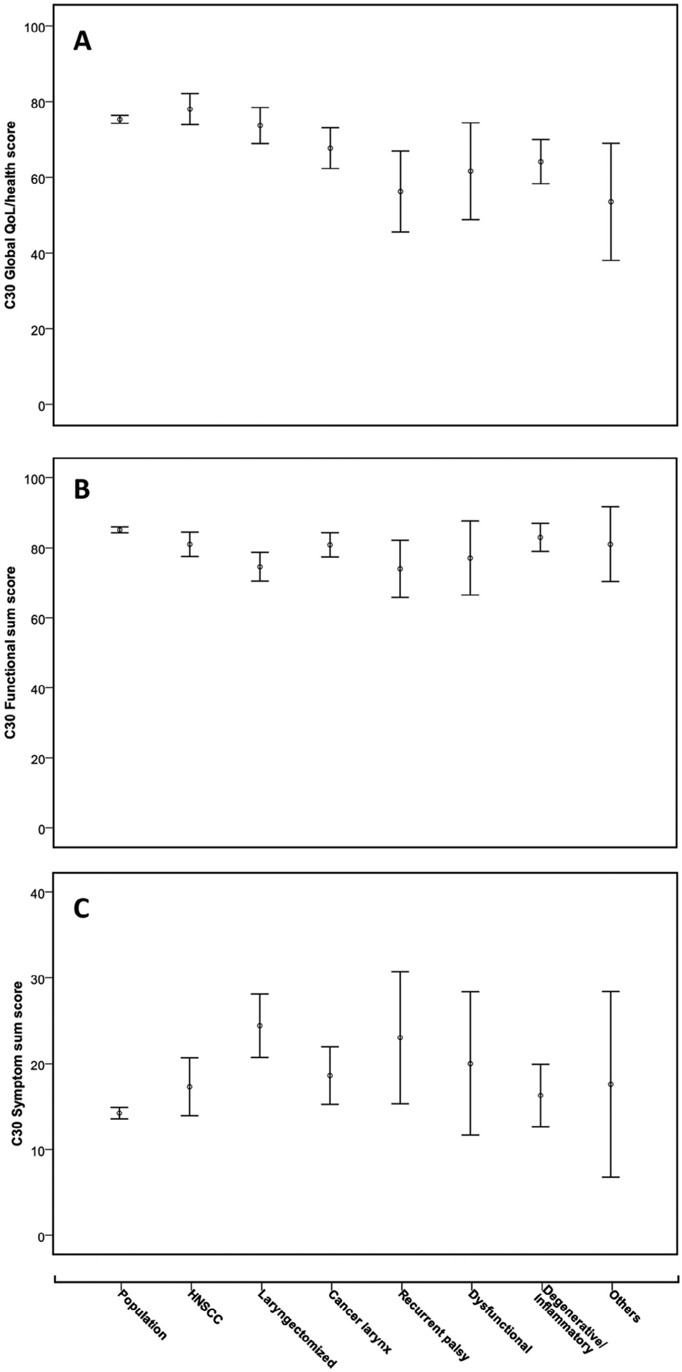
A
C30 Global QoL/health score
100
80
60
40
20
0
B
C30 Functional sum score
100
80
60
40
20
0
C
C30 Symptom sum score
40
30
20
10
0
Population
HNSCC
Laryngectomized
Cancer larynx
Recurrent palsy
Dysfunctional
Degenerative/
inflammatory
Others

FIGURE 1. Patients with larynx disease *versus* patients with head and neck squamous cell carcinoma (HNSCC) *versus* general population (sum scores):
European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ)" (**A**) general quality of life (QoL)/health, (**B**) C30 sum functional, (**C**) C30 sum symptom.
Answers were given according to a 4-point Likert format, except for questions about general health and quality of life, which were given according to a 7-point Likert format. The functional indexes (from population) of the C30 version 2.0 were scored according to a 2-point Likert format. The C30 functional scales and the global scale were transformed so that 100% indicates best function and 0% indicates least function of the individual QoL index, whereas the C30 symptom scales were transformed so that 0% indicates the least and 100% indicates the most symptoms. (**B**) Sum scores of physical, role, cognitive, emotional, and social indexes. (**C**) Sum scores of fatigue, pain and nausea/vomiting, dyspnea, insomnia, anorexia, constipation, diarrhea, and financial difficulties indexes.
Statistics: Global QoL/health depending on group allocation: $F_{7,2362} = 9.47$, $P < 0.001$. *Post hoc* analyses: population > recurrence palsy and degenerative/inflammatory. Recurrence palsy < formerly treated for HNSCC and laryngectomized. Degen./inflammatory < formerly treated for HNSCC. Functional HRQoL sum score depending on group allocation: $F_{7,2327} = 7.14$, $P < 0.001$. *Post hoc* analyses: population > laryngectomized, recurrence palsy. Symptom sum HRQoL sum scores depending on group allocation: $F_{7,2381} = 8{,}13$, $P < 0.001$. *Post hoc* analyses: population < laryngectomized and recurrent palsy. Laryngectomized > formerly treated for HNSCC and degen./inflammatory.

HRQoL scores related to VHI scores (cohort I)

When analyzing the results from cohort I, we found that the correlation between the different HRQoL sum scores among the same patients was, as expected, substantial with a common variance ranging from 33% to 72% ($P < 0.001$) (Table 2). The VHI scores also correlated with the HRQoL sum scores with 12% to 20% common variance ($P < 0.001$) (Table 2). From cohort I, the different EORTC H&N35 indexes obtained also correlated with each other (Table 3). Furthermore, the VHI scores correlated closely with the "speech" index with a common variance of 52% (Figure 4). The VHI scores in addition correlated with the other obtained EORTC H&N35 indexes with a common variance varying between 2.5% and 14%, with the strongest correlation toward "feeling ill" (Table 3).

VHI scores related to age, gender, smoking history, and level of voice use (cohort I)

We observed a negative correlation between the VHI scores and the age of the patient with 3% ($P < 0.01$) common variance. About the same level of common variance was observed between VHI and gender, with women scoring lowest. No significant correlation was obtained between pack-years smoking and VHI scores when adjusted by age and gender of the patients. No systematic reported dependence on level of voice (professional/leisure) use and VHI scores (Table 4) was observed.

Importance of EPI score levels on HRQoL and VHI score levels (cohort I)

The neuroticism scores correlated with HRQoL levels, with values ranging from 22% to 23% ($P < 0.001$) (Table 2) in patients of cohort I. The VHI scores also correlated with reported level of neuroticism with a common variance of 8% ($P < 0.001$). Partial correlation analysis with neuroticism as covariate and HRQoL and VHI scores as variables furthermore showed a common variance ranging from 7% to 14%, indicating that a substantial part of the common variance of HRQoL sum scores and VHI was secondary to level of neuroticism. We also divided the patients in cohort I in two groups based on low or high level of neuroticism. A MANOVA analysis with diagnostic group as one dimension and level of neuroticism as a second dimension showed results highly dependent on both VHI score ($F_{4,228} = 6.3$; $P < 0.001$) and level of neuroticism ($F_{1,228} = 12.6$; $P < 0.001$), but there was no interaction between these dimensions ($F_{4,228} = 0.65$; $P = 0.625$) (Figure 5).

DISCUSSION

We have studied the associations between HRQoL and specific diagnoses in a cohort of patients with voice-related disease compared with a reference cohort, to patients successfully treated for general HNSCC and to previously laryngectomized patients. The results showed that in particular, patients with recurrent palsy and laryngeal cancer had lowered general HRQoL. The HRQoL variables were furthermore inversely tied to neuroticism.

The results show that the HRQoL scores were scored depending on specific laryngeal disease. In particular, three of the included groups scored with lower HRQoL than the reference population, that is, the laryngectomized patients, the patients with laryngeal cancer, and the patients with recurrent nerve palsy. It is to be expected that cancer patients score with lower HRQoL than a general cohort. Laryngectomized patients must in particular be expected to suffer from the sequels of the cancer disease.[20] Despite this, the HRQoL scores of the larynx cancer disease groups are indicated to be relatively numerically similar to that of the other disease groups studied.

We have chosen to group the specific larynx diseases based on a previous study of which diseases scored as clusters as measured by the VHI scores.[21] These groups were furthermore in general agreement with the grouping as suggested by Verdonck-de Leeuw et al[11] and Nawka et al[24] reporting from a multicenter study based on VHI scores from patients with benign larynx diseases from many different sites across Europe. As to the HRQoL scores, it is possible that if other lines to distinguish the patients are employed, there would have been sharper lines between the patient groups.

The patients with recurrent nerve palsy in particular scored with low HRQoL. Many of these patients have serious diseases,[25] and judging on this background, lowered HRQoL scores are not surprising. The symptoms characterizing this disease also inflict reduced functional capacity.[25] In line with this, Rosen et al[26] have, for example, found that among patients with larynx disease, worst

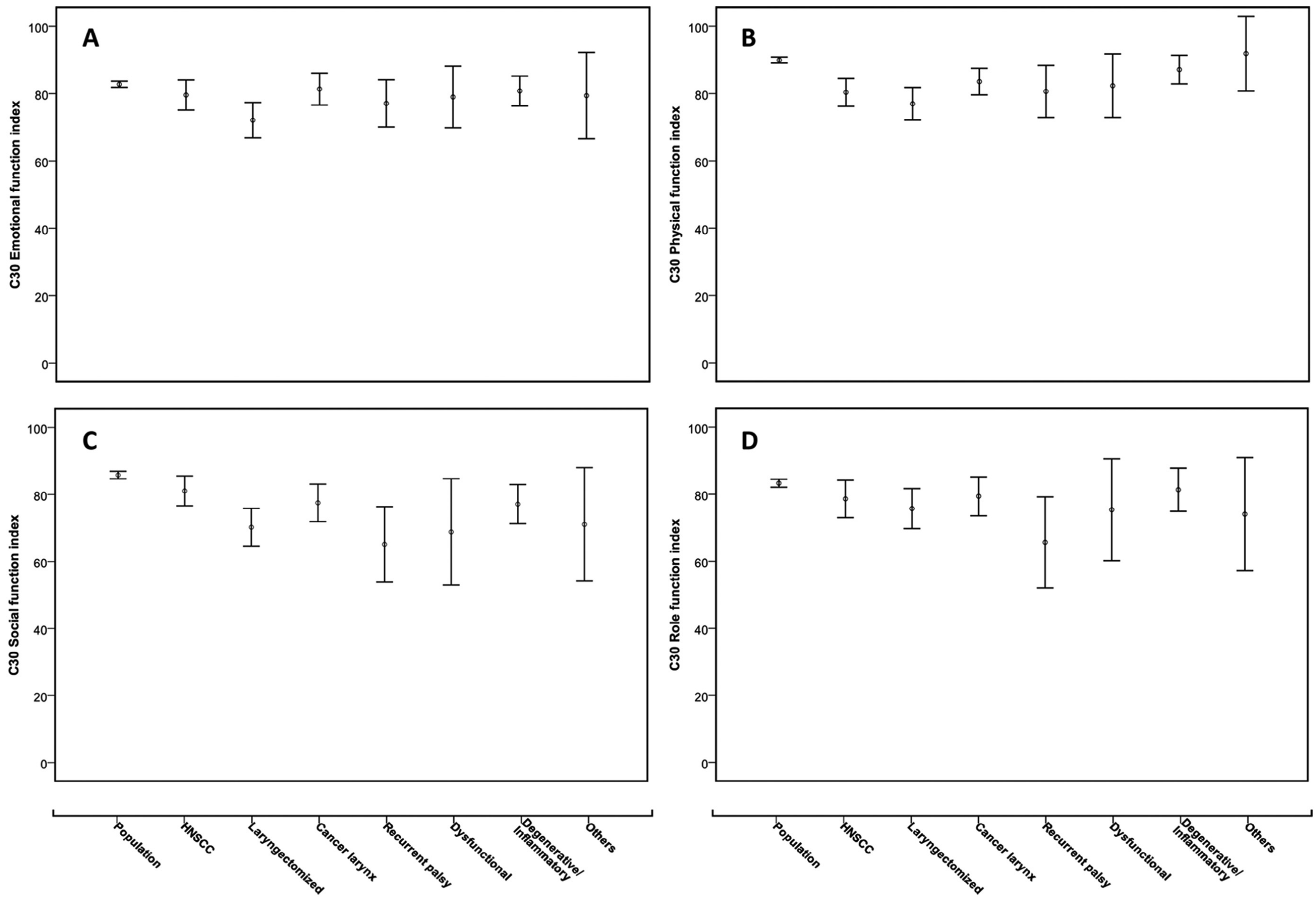

FIGURE 2. Patients with larynx disease *versus* patients with head and neck squamous cell carcinoma (HNSCC) *versus* general population (functional indexes): (**A**) C30 emotional index, (**B**) C30 physical index, (**C**) C30 social index, and (**D**) C30 role index.
EORTC QLQ C30 functional indexes were used. Scores were calculated as given in Figure 1 legend.
Statistics: Emotional index depending on group: $F_{5,2264} = 5.74$, $P < 0.001$. Laryngectomy < all other groups. Physical index depending on group: $F_{7,2210} = 12.2$, $P < 0.001$. *Post hoc* analyses: Population > laryngectomy, patients formerly treated for HNSCC; laryngeal cancer. Degen./inflammatory > laryngectomized. Social index depending on group: $F_{7,2210} = 13.6$, $P < 0.001$. Population > all other groups except group formerly treated for HNSCC. Role index depending on group: $F_{7,2284} = 6.7$, $P < 0.001$. *Post hoc* analyses: population > recurrence palsy.

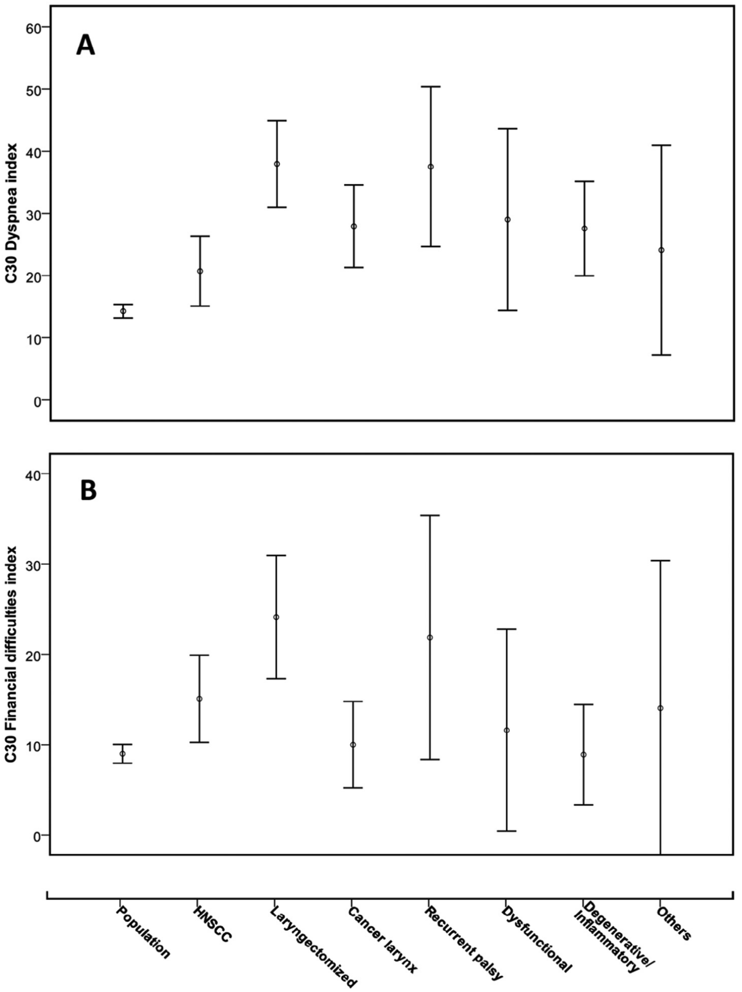

FIGURE 3. Patients with larynx disease *versus* patients with head and neck squamous cell carcinoma (HNSCC) *versus* general population (symptom indexes):

EORTC QLQ C30 indexes were used. Scores are calculated as given in Figure 1 legend.

(**A**) C30 dyspnea, (**B**) C30 financial strain.

Statistics: Dyspnea index scores depending on group: $F_{7,2288} = 24.4$, $P < 0.001$. *Post hoc* analyses: Population < all other groups except group formerly treated for HNSCC and degen./inflammatory group. Laryngectomized and recurrent palsy > patients formerly treated for HNSCC. Financial strain index dependent on group: $F_{7,2288} = 7.6$, $P < 0.001$. *Post hoc* analyses: population < laryngectomized and recurrence palsy.

VHI scores were obtained from those with unilateral vocal fold paralysis. Helidoni et al[27] and Lam et al[28] have furthermore determined in their studies of patients with larynx disease that the neurogenic group had the worst VHI scores. The present results, together with the abovementioned studies, support that patients with recurrent palsy as a group suffer broadly reduced HRQoL.

The HRQoL scores were not generally dependent on gender or age of the included subject. This is also supported by findings from other studies.[27,29] We have, however, determined a negative correlation between age of the patients and VHI scores. This is interesting and needs further investigation. Patients were asked to report whether they are smoking. We have not determined any specific effect of smoking directly on the HRQoL scores.

Patients with degenerative or inflammatory benign disease scored lower than the reference population in the global QoL/health score. Thus, having these limited larynx diseases had an

TABLE 2.
Correlation Matrix Between Sum Scores Derived From the General (C30) EORTC QLQ, VHI, and EPI Scores Among Patients With Voice Disease (Cohort I)

	Voice Handicap Index	General Health/QoL	Function QoL Sum	Symptom QoL Sum	EPI Neuroticism	EPI Extraversion
General health /QoL	−.42***					
Functional QoL sum	−.45***	.63***				
Symptom QoL sum	.35***	−.58***	−.85***			
EPI neuroticism	−.28***	.47***	.47***	−.48***		
EPI lie	.03	−.10	−.02	.04	−.23***	
EPI extraversion	.10	−.21***	−.19**	.16*	−.18**	−.08

* $P < 0.05$.
** $P < 0.01$.
*** $P < 0.001$.

TABLE 3.
Pearson Correlation Matrix Including VHI Scores and Some EORTC H&N35 QLQ Indexes Among Patients With Voice Disease (Cohort I)

	VHI	Speech	Teeth Problems	Open Mouth	Dry Mouth	Sticky Saliva	Coughing
Speech	.72***						
Teeth problems	.09	.16*					
Open mouth	.19**	.07	.22***				
Dry mouth	.16*	.215***	.38***	.291***			
Sticky saliva	.18**	.29***	.32***	.26***	.56***		
Coughing	.26***	.37***	.17**	.07	.31***	.47***	
Feeling ill	.37***	.40***	.14*	.17*	.26***	.30***	.45***

* $P < 0.05$.
** $P < 0.01$.
*** $P < 0.001$.

impact on the general well-being of the patients. Furthermore, the symptom index “dyspnea” from the general EORTC QLQ was in particular scored depending on larynx disease. Secondary analyses even suggested that alleviating dyspnea would remove most of the impact of larynx disease on HRQoL. Larynx airway obstruction as a key feature of larynx disease should thus be further studied. This also supports the need for treatment of patients with larynx disease. The often relatively simple

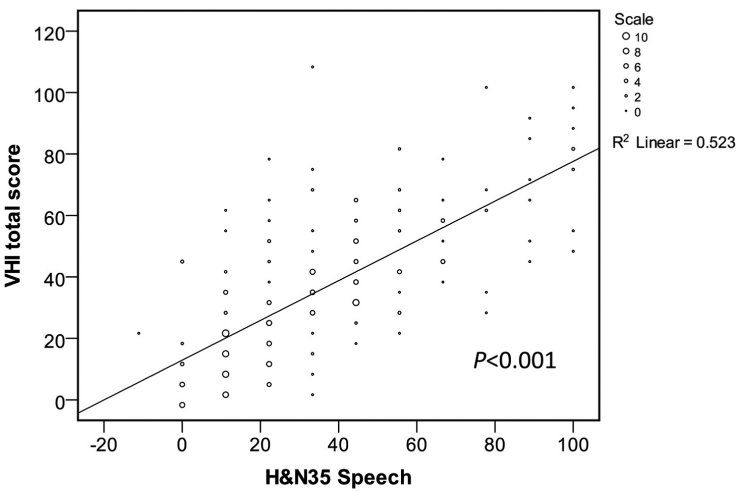

FIGURE 4. Scatter plot from VHI sum scores *versus* EORTC H&N35 “speech” index.

TABLE 4.
Correlation Scores (Pearson) Between Reported EORTC C30 QLQ/VHI Scores and Age, Gender, as well as Reported Speech Difficulty, Amount of Voice Use, and Pack-years of Smoking Among Patients With Voice Disease (Cohort I)

	VHI	General Health/QoL	Functional QoL Sum	Symptom QoL Sum
Age	−.17**	.04	.09	−.04
Gender	−.17*	.09	.14*	−.13
Speech difficulty	.67***	−.39***	−.34***	.27***
Professional use of voice	.03	.12	.10	−.15*
Leisure use of voice	.03	.04	.05	−.04
Smoking (pack-years)	−.13*	−.04	−.03	.04

* $P < 0.05$.
** $P < 0.01$.
*** $P < 0.001$.

treatment of such diseases may thus give excellent global HRQoL yield.

We have determined that the level of financial strain was scored depending on larynx disease. In particular, the laryngectomized patients and the patients with recurrent nerve palsy reported higher scores on such strain. The fact that such questions give useful answers should encourage including these matters in the follow-up of patients with laryngeal disease.

The VHI scores correlated closely with the EORTC QLQ index "speech." This may be viewed as an additional strong argument that the VHI scores resemble a symptom-specific HRQoL variable. These results are to some extent surprising as the VHI asks to a large extent about voice disability in a social context. One could possibly conclude that the framing of a question is less important than the factual information the questions are asking about. This should be more closely studied.

This study has weak points. First, it is a cross-sectional study. Furthermore, some of the information about the social conditions of the included patients should be obtained as degree of social support is associated to HRQoL.[30] It is also missing information about present comorbidities of the included patients, which is important as such conditions are known to influence the HRQoL scores.[31]

It should be noted that some of the groups show large HRQoL standard deviations, indicating that matters other than the specific diagnosis contribute to the HRQoL scores. Level of neuroticism is known to have a major impact on HRQoL scores in various patient groups.[32] Thus, it is of relevance to determine this impact when acquiring HRQoL of patients with larynx disease. We have shown that level of neuroticism was correlated to the HRQoL scores and to VHI scores with a substantial common variance. In addition, some of the common variance between the HRQoL and the VHI scores were secondary to level of neuroticism. The impact of neuroticism on the VHI scores in addition strengthens the view that the VHI score may be classified as a HRQoL score.

Among the patients with larynx disease, the EORTC-H&N35 "speech" index in particular was scored with a close association to the VHI score. This suggests that the VHI questionnaire may

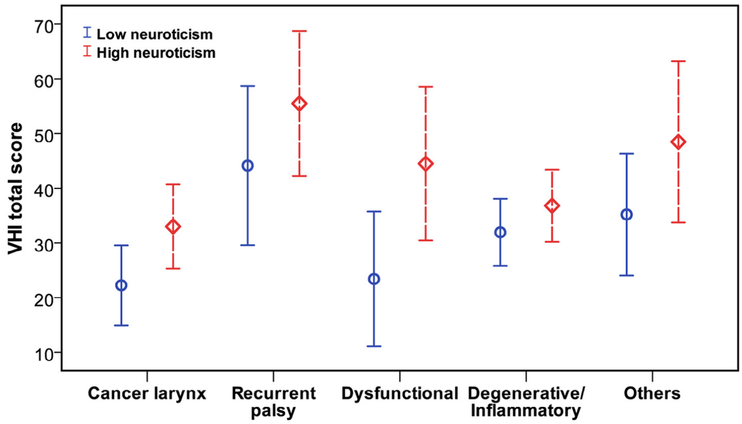

FIGURE 5. VHI scores depending on low *versus* high neuroticism scores *versus* larynx diseases.
Blue circles = low neuroticism; red diamonds = high neuroticism.
Statistics: MANOVA analysis with group as one dimension and level of neuroticism as a second dimension showed results highly dependent on both VHI score ($F_{4,228} = 6.3$; $P < 0.001$) and level of neuroticism ($F_{1,228} = 12.6$; $P < 0.001$), but there was no interaction between these dimensions ($F_{4,228} = 0.65$; $P = 0.625$). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

be used generally in conjunction with the EORTC QLQ when the EORTC-H&N35 speech index is scored with a high value in order to validate this score.

The present investigation underlines the importance of voice in larynx disease as associated also to general HRQoL, and suggests that voice patency contributes substantially to the generation of good HRQoL, at least in patients with larynx disease, which in turn further strengthens the view that voice-improving treatments generate better HRQoL among patients with larynx disease.

This study shows that HRQoL scores may yield information when included in clinical routine laryngological consultations. Some of the differences between the groups reached 10 HRQoL points, which is consistent with being of clinical relevance.[33] A general HRQoL questionnaire will provide additional information about the patient and is therefore recommended to be included as part of a complete investigation of patients with voice disease.

CONCLUSIONS

We have shown among patients with larynx disease that, in particular, cancer patients and patients with recurrent palsy had lowered general HRQoL. The general EORTC QLQ and the VHI, as voice-specific HRQoL measures, may be recommended in the standard protocol for assessment of patients with voice disease.[1]

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IV

Acoustic Voice Analysis and Maximum Phonation Time in Relation to Voice Handicap Index Score and Larynx Disease

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Summary: Objectives. Patients with voice-related disorders are ideally treated by a multidisciplinary team. Acoustic voice analysis and patient-reported outcome measures are recommended parts of the clinical assessment. The present paper aims at further documenting the importance of acoustic voice analyses, maximum phonation time (MPT) and Voice Handicap Index (VHI) into clinical investigations.

Study design. The participants (N = 80 larynx cancer, N = 32 recurrent palsy, N = 23 dysfunctional, N = 75 degenerative/inflammation (N = 19 various excluded)) were included consecutively at the outpatient laryngology clinic at Haukeland University Hospital. In addition, a control group of 98 healthy subjects were included.

Method. Voice samples, MPT, and the VHI scores in addition to standard clinical information were obtained. Acoustic analyses were performed from these samples determining level of jitter, shimmer and Noise-to-Harmonic ratio (NHR) as well as analyzing frequency of a prolonged vowel.

Results. Jitter, shimmer, and NHR scores correlated strongly ($r \approx 0.8$; $P < 0.001$) to each other. By Analysis of Variance analyses, we have determined significant dependence on diagnostic group analyzing all the obtained acoustic scores (all $P < 0.001$). All patient groups but the dysfunctional group scored to some extent worse than the control group (mostly at $P < 0.001$). In addition, jitter scores from dysfunction group were lower than recurrent palsy group ($P < 0.05$) and shimmer scores were lower among dysfunctional than the cancer group ($P < 0.05$). Regarding NHR the cancer patients scored higher than the degenerative/inflammatory group ($P < 0.05$). The cancer group scored with longer MPT than the degenerative/inflammatory ($P < 0.001$) and recurrent palsy groups ($P < 0.05$).

Conclusion. Among larynx disease patients acoustic and MPT analyses segregated with all determined analyses between patients and control conditions except the dysfunctional group, but also to some extent between various patient groups. VHI scores correlated to jitter, shimmer and NHR scores among cancer and degenerative/inflammatory disease patients. Acoustic analyses potentially add information useful to laryngological patient studies.

Key Words: Acoustic voice analysis–Maximum phonation time–Voice handicap index–Norwegian–Voice disorders.

INTRODUCTION

The European Laryngological Society (ELS) has proposed a basis protocol for assessment of voice-related diseases[1] which recommends including assessment by acoustic analysis, aerodynamics, and patient-reported outcome measures (PROM). This ELS protocol encourages comparing patients with voice-related diseases by measurement of the voice physical function in order to assess the importance of such measurements when assessing patients with voice-related disease.[1,2] Such data should aid to study voice characteristics stringently and support to discriminate between various larynx diseases, as well to assess treatment efficiency. There is still a need to study the benefit of employing acoustic parameters in relation to diagnosis and treatment of voice-related diseases.[3,4] A goal of all, laryngological inclusive, patient treatment is to improve PROM scores to normal level values.[5] In order to do so it is of interest to study to what extent acoustic physical analyses can point to important matters regarding associations to the PROM scores.

One theory behind acoustic analyzes of voice has been that the changes in vocal fold mass, or tension leads to increased and measureable irregularity or noise in the sound of the voice sample.[6,7] Noise could be defined as random aperiodic energy in the voice,[8] and may have two main causes. It could be a sources of noise near, or at the vocal folds, (ie, the airstream between the vocal folds), or a significant aperiodicity in the glottis wave of the vocal folds.[8] The ELS protocol recommends fundamental frequency (F0), relative jitter, and shimmer as pertinent parameters[1] of acoustic analysis. The ELS also suggests Noise-to-Harmonic ratio (NHR) as a robust acoustic measure,[1] but points out a lack of standardizing among different analyzing methods regarding this parameter.[1] These four parameters are the commonly used parameters within acoustic analysis of voice samples[6,9,10]; and thus employed in this study.

Voice frequencies deviation (jitter) or voice amplitude deviation (shimmer) quantifies the unintentional irregularity of the sound waves.[9] Jitter, also known as frequency perturbation, measures the variation from the cycle-to-cycle

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within the fundamental frequency of a voice signal.[7,8] Shimmer, known as amplitude perturbation, measures the variation from the cycle to cycle within the amplitude.[9] Studies which have combined several different acoustic parameters and visual examination of the larynx suggest jitter and shimmer to be valuable in the characterization of voice pathology.[11,12] NHR represents a global measure of noise in the voice sample.[13] Irregularity of the acoustic measures may to some degree viewed as normal variation, and this variation may be depended on gender, age, language, and culture.[14-17] This has to be kept in mind during studies of acoustic parameters in voice pathology.

Fundamental frequency (F0) is a measure of the lowest detectable frequency of the voice. The frequency of a sound is defined as number of complete oscillations per second. In the human voice this corresponds to number of complete open-close cycle of the vocal folds per second. The ELS protocol recommends fundamental frequency (F0) and the fundamental frequency has been determined by Wuyts et al to be associated with VHI values[8] and thus should be an interesting parameter to include within voice analyses.

Maximum phonation time (MPT) is an aerodynamic parameter, and according to the ELS protocol, the easiest and most common used technic to measure aerodynamics in voices.[1] MPT reports the maximum length of a continuous phonation of a vowel in seconds. Inadequate closure of the vocal folds would give a short MPT due to increased air leakage through rima glottidis. Studies have found correlation between low MPT and pathology of the larynx.[18,19] An aim of this study has also been to further investigate the possible associations between MPT, acoustic analysis, and voice disorders.

Several PROMs aimed at measuring the specific impact of voice-related diseases on activities of daily life have been developed.[20] The Voice Handicap Index (VHI) constitutes one such example and includes questions measuring various perceived consequences of voice disease. The Agency for Health Care Research and Quality reported in 2002 that the VHI met stringent criteria for reliability, validity, and availability of normative data.[21] Verdonck-de Leeuw et al.[22] have validated the VHI by assessing equivalence of European translations of the questionnaire to the following languages: German, French, Dutch, Italian Portuguese, Belgian, and Swedish.[22] A Norwegian translation has also been published.[23] Several investigators have utilized VHI scores in order to study effects of larynx disease treatment.[24-26] Studies have suggested that VHI score levels correlate with acoustic measures.[27] It has been an aim of the study to investigate the relation between acoustic measures, MPT, and VHI.

It should furthermore be of interest to study the acoustic variable scores in healthy control persons, and this has been one major aim of the present investigation to gather a control group and to compare such scores with the various patient groups. In particular, it seems to be of interest to study to what extent functional disease acoustic measures differ from control conditions.

Acoustic parameters derived from voice samples should have the ability to discriminate between controls and different laryngological diseases.[28] Our primary aim has been to study in more detail the ability of acoustic parameters to differentiate between various laryngological diseases contrasted to healthy controls. Our secondary aim has been to study fundamental frequency, jitter, shimmer, NHR, and MPT value correlations to VHI both generally including a healthy control group, and at an individual disease level.

MATERIAL AND METHODS

Participants

Cohort of Haukeland University Hospital (HUH) voice-diseased patients

These participants (N = 229) consisted of 138 men (median age 61, range 24-86) and 91 women (median age 51, range 18-79) and were included consecutively following appointments at the laryngology clinic at HUH. The clinic receives both patients referred from family physicians and from surrounding private practice ENT specialists. The patients received the questionnaires in an envelope at the consultation and return the questionnaires by mail after filling out answers at home. The return-rate of the questionnaires was 81%. The patients were subjected to standard medical and voice therapist examination according to the standard procedure suggested by ELS.[1] The diagnostic groups were set according to a previously published flow chart.[28] In short, the recurrent palsy patients all had the vocal cords in classical para-median position. Nineteen had palsy on the left and 13 on the right side. The cancer patients had all previously been treated because of laryngeal cancer. The degenerative/inflammatory group consisted of patients with Reinke edema (16), laryngitis (16), polyp (17), cyst (12), papilloma (8), and nodules (6). Patients with dysfunctional disease were patients with symptoms caused by misuse of the voice box, but without any physical pathology visible by laryngoscopy. The characteristics of the presently included patients are given in Table 1. The patients have also formed the basis for two previous publications. More details about the patients may be gathered form these publications.[28,29]

Control group

The control group consisted of 106 healthy volunteers recruited by information posters and letters distributed to the hospital, university employees, and students. The inclusion criteria were that they signed an informed consent, were above 18 years of age, underwent video-laryngo-stroboscopy, recorded a successful voice sample, and answered the VHI questionnaire. Furthermore, cognitive functions and language skill needed to answer the VHI questionnaire intelligible in Norwegian were required. If the controls were diagnosed with larynx pathology at the video-laryngo-stroboscopy, they were excluded from the study. Eight participants were excluded either due to findings of larynx pathology, did not complete the examination or had missing

TABLE 1.
Age, Voice Handicap Index (VHI) Sum Score, F0, Jitter, Shimmer, Noise-To-Harmonic Ratio (NHR), and Maximum Phonation Time (MPT) With Mean, Range, SD and Number of Controls and Patients in Diagnosis Groups

	Controls				Cancer				Rec palsy				Dysfunctional				Degen/inflam*			
Parameter	M	Range	SD	n	M	Range	SD	n	M	Range	SD	n	M	Range	SD	n	M	Range	SD	n
Age	33.84	19–74	13.82	98	66.48	37–85	10.14	80	56.60	34–79	11.02	32	50.54	29–77	15.01	23	51.65	20–86	14.68	73
Female	35.00	22–74	14.34	65	60.20	41–74	12.90	7	58.84	41–79	10.56	16	47.62	29–68	13.96	15	50.44	20–75	15.55	39
Male	31.55	19–63	12.62	33	67.09	37–85	9.73	73	54.36	34–69	11.34	16	56.02	32–77	16.55	8	53.05	27–86	13.71	34
VHI	9.12	0–33	7.83	98	27.51	0–101	23.54	80	50.47	5–100	26.31	32	35.09	4–84	22.72	23	35.25	3–84	19.09	73
Female	7.85	0–26	6.77	65	55.43	5–101	37.60	7	48.75	5–85	22.38	16	40.07	5–84	23.68	15	30.97	8–74	17.50	39
Male	11.64	0–33	9.18	33	24.84	0–82	20.18	73	52.19	17–100	30.39	16	25.75	4–56	18.66	8	40.15	3–84	19.91	34
MPT	16.14	5–34	6.17	98	17.10	3–45	8.63	77	12.73	2–32	7.65	31	16.22	6–34	7.89	22	11.87	2–43	6.69	70
F0	213.53	83–440	68.95	98	184.38	86–459	64.67	77	187.68	78–323	64.62	31	202.82	116–301	51.65	22	188.07	86–438	60.73	70
Female	252.78	182–440	46.54	65	223.17	157–287	55.56	6	214.50	108–275	51.03	16	227.86	137–301	41.70	14	217.55	113–305	44.96	38
Male	136.21	83–226	28.01	33	181.10	86–459	64.65	71	159.07	78–323	66.77	15	159.00	116–226	36.40	8	153.06	86–438	58.88	32
Jitter	1.09	0,21–4,52	0.81	98	3.09	0,33–12,80	2.63	77	3.48	0,29–13,80	3.24	31	1.73	0,45–7,81	1.70	22	2.25	0,44–10,02	2.21	70
Shimmer	3.70	1,06–10,63	1.98	98	9.17	1,61–39,88	7.76	77	8.22	1,21–20,94	5.03	31	5.06	2,11–17,40	3.28	22	6.44	1,13–33,39	5.59	70
NHR	0.14	0,04–1,13	0.11	98	0.24	0,07–1,09	0.18	77	0.22	0,07–0,73	0.15	31	0.16	0,08–0,58	0.10	22	0.18	0,09–0,67	0.11	70

* *Degn/inflam=Degenerative/inflamatoric, concist of Reinke edema(16), laryngitis(16), polyp(17), cyst(12), papilloma(8) and nodules(6).*

VHI questionnaire. This constitutes 8.5% dropout, and a total of 98 participants were included in the study, median age 34 years and range 19-74 years. Thirty-tree males, median age 32 year, range 19-63 years, and 65 women, median age 35 year, range 22-74 years were included.

Voice samples

Voice recordings were obtained from both patients and controls at the laryngology clinic at HUH. The voice recordings were obtained computer based through a standardized procedure in a small sound proof (insulated) room with the use of software from Key Elemetrics, Multi Speech model 3700 and Multi-Dimensional Voice Program model 5105. The Shure SM 81 condenser microphone with mounted pop-filter was placed 30 cm in front of the subjects at an angle of 35°. The recording box was dedicated to the purpose and designed to limit surrounding noise. Instructions were thoroughly given to ensure that all the recordings were performed according to the standardized procedure with equal distance from the microphone. The subjects were first producing a prolonged vocal /A/, then reading of a standardized text (The north wind and the sun), and lastly repeating the prolonged vocal /A/. The technically judged best performance of the prolonged vocal /A/ was chosen, from which both the acoustic analysis and MPT were obtained. This was usually the lastly obtained vowel. In the acoustic analysis the midsection of the prolonged vocal was used. The software Multi-Dimensional Voice Program (MDVP) from Kay Elemetrics was also used to analyze the voice samples. The parameters F0, Jitter (jitt %), Shimmer (shim %), and NHR and maximum phonation time (MPT) were reported.

The Voice Handicap Index

Both patients and controls answered the Norwegian VHI.[23] VHI includes 30 statements (items).[30] The answers are given according to a five point Likert scale (from 0 = never to 4 = always). The total VHI sum score ranges from 0 to 120 points. The highest value represents maximum level of perceived voice handicap.

Additional questionnaires utilized

The patients answered in addition questions about background information regarding occupation, a visual analogue scale (VAS) stating how seriously the voice disease was perceived as well as a 5 or 6 point Likert scale about level of voice use (1 = quiet listener . 6 = extremely talkative) both at home and at work.

Statistics

We used a commercially available statistical program package (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 24.0 Armonk, NY: IBM Corp). Statistical significance was considered if $P < 0.05$. All P values reported represent two-sided tests. Pearson correlation, linear regression analysis and analysis of variance (ANOVA) analyses followed by post hoc tests (Bonferroni method) were calculated as indicated.

RESULTS

Acoustic score and MPT relations to age and gender of the included subjects

The characteristics of the presently included patient data are given in Table 1. All the determined acoustic scores were on group level dependent on gender of the included subjects (Table 2). In particular, F0 ($r = 0.57$; $P < 0.001$) showed strong dependence. Likewise, all acoustic scores but the MPT were scored dependent on age of the subject. The highest correlation was shown to jitter/shimmer (both $r \approx 0.31$; $P < 0.001$) (Table 2).

Acoustic scores and MPT intercorrelation

All the determined acoustic scores inter-correlated significantly. The highest values were determined between level of shimmer and jitter ($r = 0.81$; $P < 0.001$). The NHR also correlated closely to the shimmer/jitter level ($r = 0.81/0.75$; $P < 0.001$) (Table 2).

Acoustic scores and MPT related to diagnoses

We have determined a dependence of disease group when analyzing the jitter values dependent on diagnosis by ANOVA analysis ($F_{4,297} = 13.3$; $P < 0.001$) (Fig. 1). When subjected to Bonferroni post hoc analyses, the controls scores were lower than the cancer ($P < 0.001$), the recurrent palsy ($P < 0.001$), and the degenerative/inflammatory ($P < 0.01$) groups. In addition, the dysfunctional group scored lower than recurrent palsy group ($P < 0.05$). The shimmer analysis also showed a dependence of group by ANOVA analysis ($F_{4,297} = 13.1$; $P < 0.001$) (Figure 1). When subjected to Bonferroni post hoc analyses, the controls scored lower than the cancer ($P < 0.001$), the recurrent palsy ($P < 0.001$), and the degenerative/inflammatory ($P < 0.01$) groups. In addition, the dysfunctional group scored lower than the cancer group ($P < 0.05$) and the cancer group scored higher than the degenerative/inflammation group ($P < 0.05$). When performing the ANOVA analysis with gender and age of the patient included as co-variate the analyses still determined a dependence on jitter and shimmer scores on group.

NHR was also scored dependent on diagnosis by ANOVA analysis ($F_{4,297} = 7.0$; $P < 0.001$) (Figure. 1). By Bonferroni post hoc analyses the controls scored lower than the cancer ($P < 0.001$) and the recurrent palsy ($P < 0.05$) patients. Cancer patients in addition scored higher than the degenerative and inflammatory patients ($P < 0.05$).

MPT was measured and scored dependent on group by ANOVA analysis ($F_{4,297} = 6.4$; $P < 0.001$) (Figure 1). When applying Bonferroni post hoc analyses to diagnosis, the controls scored with longer duration than the degenerative-inflammatory group ($P < 0.01$). In addition, the cancer group scored with longer duration than the recurrent palsy ($P = 0.05$) and the degenerative/inflammatory group ($P < 0.001$). When performing the ANOVA analysis with gender and age of the patient included as co-variate the analysis still determined a dependence of MPT on group.

An ANOVA analysis was performed with F0 as dependent variable and diagnosis and gender as independent variables. This analysis showed a significant dependence on gender ($F_{4,297} = 72.4$; $P < 0.001$), but not on diagnosis. A significant interaction between gender and diagnosis ($F_{4,297} = 4.3$; $P = 0.02$) was on the other hand observed. Therefore, F0 dependent on diagnosis was analyzed separated by gender. Including males only ANOVA showed that F0 was scored dependent on diagnosis ($F_{4,159} = 3.9$; $P = 0.005$) (Figure 2). When subjected to Bonferroni post hoc analyses, the male cancer patients scored lower frequency than the controls ($P < 0.01$).

TABLE 2.
Correlation Between Maximum Phonation Time (MPT), F0, Jitter, Shimmer, Noise to Harmonic Ratio (NHR), Gender, Age and Reported Degree of Voice Problems/Voice Use

	MPT	F0	Jitter	Shimmer	NHR	Age
Maximum phonation time (MPT)						
F0	−.24***					
Jitter	−.30***	.12*				
Shimmer	−.26***	.12*	.81***			
NHR	−.18**	.15**	.75***	.80***		
Age	n.s.	−.13*	.32***	.31***	.24***	
Gender	−.29***	.57***	−.16***	−.15**	−.11*	−.30***
Degree of voice problems (patients)	−.29***	n.s.	−.23***	n.s.	n.s.	.17**
Degree of voice use (patients)	n.s.	n.s.	−.26***	−.27***	−.26***	−.31***

* Correlation significant at 0.05 level.
** Correlation significant at 0.01 level.
*** Correlation significant at 0.001 level.
n.s.: not significant.

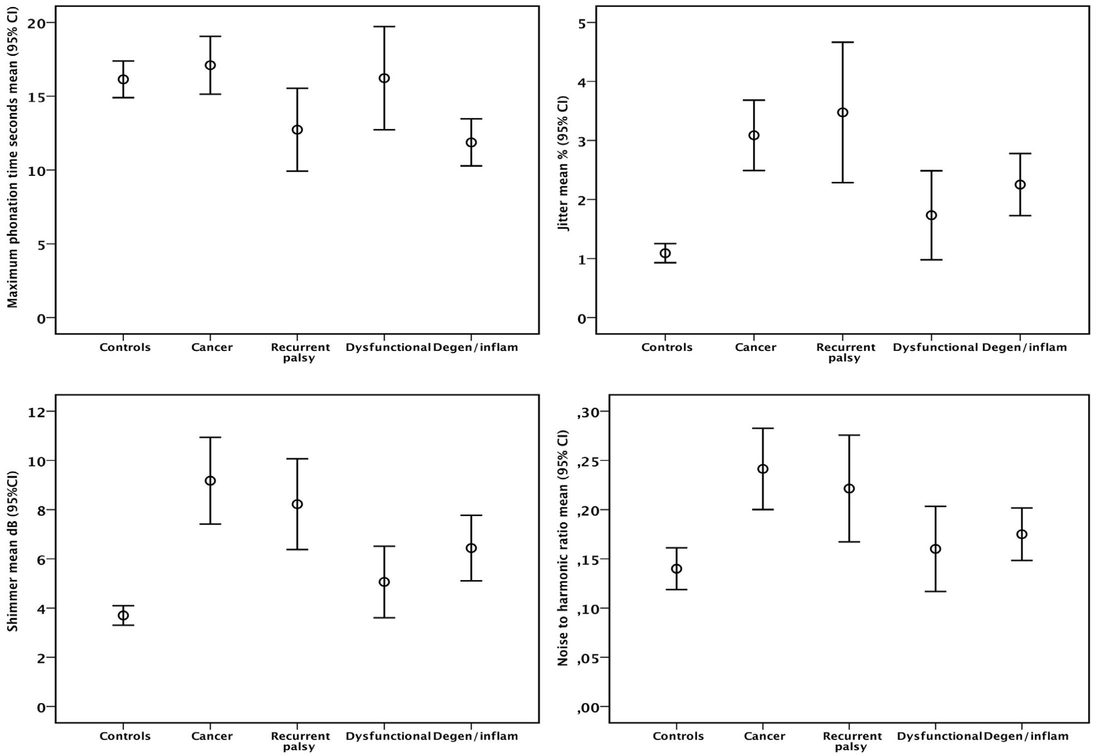

FIGURE 1. The jitter, shimmer, noise to harmonic ratio (NHR) and maximum phonation time (MPT) scores (mean ±confidence interval) dependent on group.

Groups: Controls (n = 98), cancer (n = 77), recurrent palsy (n = 31), dysfunctional (n = 22), degenerative/inflammatory (n = 70).

Jitter by ANOVA ($F_{4,297} = 13.3$; $P < 0.001$). Post hoc: controls < cancer ($P < 0.001$), controls < recurrent palsy ($P < 0.001$) controls < degenerative/inflammatory ($P < 0.01$), dysfunctional < recurrent disease ($P < 0.05$).

Shimmer by ANOVA: $F_{4,297} = 13.1$; $P < 0.001$) (Fig. 1. Post hoc: controls < cancer ($P < 0.001$), controls < recurrent palsy ($P < 0.001$), controls < degenerative/inflammatory ($P < 0.01$), dysfunctional < cancer group ($P < 0.05$), cancer > degenerative/inflammation ($P < 0.05$).

NHR by ANOVA: $F_{4,297} = 7.0$; $P < 0.001$. Post hoc: controls > cancer ($P < 0.001$), controls > recurrent palsy ($P < 0.05$), cancer > degenerative/inflammatory ($P < 0.05$).

MPT by ANOVA: $F_{4,297} = 6.4$; $P < 0.001$. Post hoc: controls > degenerative-inflammatory ($P < 0.01$), cancer > recurrent palsy ($P = 0.05$), cancer > degenerative/inflammatory ($P < 0.001$).

When including females ANOVA showed that female F0 values were scored dependent on diagnosis ($F_{4,138} = 4.7$; $P = 0.001$) (Figure 2). Studied by Bonferroni post hoc analyses the controls scored with higher frequency than the recurrent palsy ($P < 0.05$) and the degenerative/inflammatory female patients ($P < 0.01$).

Acoustic analyses and MPT scores correlated to VHI scores

The different acoustic analyses numerical values did not correlate with the VHI scores among the controls (results not shown). Among all included patients, the VHI scores were associated to MPT, jitter, shimmer, and NHR with common variance ranging from 4% to 10% (all $P < 0.001$) (Table 3). If the association between VHI and the acoustic measurements were analyzed by disease group, significant correlations were shown primarily within the cancer and degenerative/inflammatory patient groups (Table 3). Subsequently stepwise regression analyses was performed including the cancer and inflammatory/degenerative "group" patient studying males and females separately (Table 4). Age of the patients, level of MPT, F0, jitter, shimmer, and NHR were included.. Both among males and females age of the patient and jitter levels were associated to VHI scores. With males MPT and with females NHR was uniquely associated to the VHI scores (Table 4).

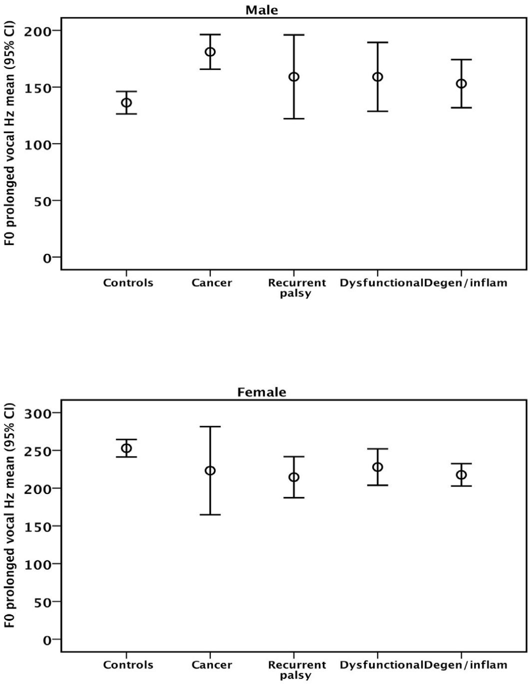

FIGURE 2. The F0 scores (mean ±CI) dependent on diagnostic group separated by gender.
Groups: Controls (n = 98), cancer (n = 77), recurrent palsy (n = 31), dysfunctional (n = 22), degenerative/inflammatory (n = 70).
Males by ANOVA: $F_{4,159} = 3.9$; $P = 0.005$. Post hoc analyses: Controls < cancer ($P < 0.01$). **Females** by ANOVA: $F_{4,138} = 4.7$; $P = 0.001$. Post hoc analyses: Controls > recurrent palsy ($P < 0.05$), controls > degenerative/inflammatory ($P < 0.01$).

Acoustic analyses and MPT scores correlated to reported degree of voice problems and voice use

Among the controls, no significant correlation was determined between the acoustic measures and the perceived degree of voice problem. Among the patients, numerical reported degree of voice problems correlated inversely with MPT (r = −0.29; $P < 0.001$) and jitter level (r = −0.23; $P < 0.001$) (Table 2), and broken down on diagnostic group similar, but weaker associations were shown than as the VHI analysis results. Furthermore, among patients reported degree of voice use correlated inversely with level of jitter, shimmer and NHR (r ≈ −0.26; $P < 0.001$) (Table 2).

TABLE 3.
Correlation Between VHI Total Score and Maximum Phonation Time (MPT), F0, Jitter, Shimmer and Noise to Harmonic Ratio (NHR) Among All Patients, and Dependent on Cancer or Degenerative and Inflammatory Diagnosis

	VHI		
	All patients	Cancer patient group	Degen. Infl. patient group
MPT	−.29***	−.39***	n.s.
F0	n.s.	.28*	n.s.
Jitter	.31***	.35**	−.41***
Shimmer	.23***	.28*	−.42***
NHR	.23***	.31**	−.51***

* Correlation significant at 0.05 level.
** Correlation significant at 0.01 level.
*** Correlation significant at 0.001 level.
n.s.: not significant.

DISCUSSION

By employing standard acoustic physical measures as suggested by ELS[1,4] we have studied the dependence of the acoustic voice variables scores on diagnosis as well as correlation to VHI scores of laryngological diseased patients as well as healthy control persons. All patient groups, except patients with functional disease, scored different acoustically from the control conditions. Jitter, shimmer, and NHR scores correlated closely. These parameters were furthermore the acoustic parameters best differentiating

TABLE 4.
Stepwise Linear Regression Analysis With "Cancer" and "Inflammatory/Degenerative" Group Patient VHI Scores as Dependent Variable and Jitter, Shimmer, Noise to Harmonic Ratio (NHR), Maximum Phonation Time (MPT), and Prolonged Vowel (F0) as Independent Variables

	Males				Females		
	Standardized coefficients Beta	t	Sig.		Standardized coefficients Beta	t	Sig.
(Constant)		5.06	0.000	(Constant)		3.75	0.001
MPT	−0.29	−2.72	0.008	Jitter	1.10	6.41	0.000
Age	−0.29	−3.07	0.003	NHR	−0.52	−3.02	0.007
Jitter	0.24	2.29	0.025	Age	−0.31	−2.60	0.018
Adjusted R^2	0.23				0.70		

between the laryngological diagnoses. The results furthermore showed around 10% common variance between VHI scores and the acoustic variable scores among the patients; mostly among cancer and degenerative and inflammatory patients.

Several limitations, however, are present in this investigation. First, the data are gathered at one time point only. Second, the study could have included more patients. If so, the ability to differentiate between specific diagnoses could then have been bettered. Third, the acquisition of acoustic analyses may vary between acquisition systems, computer software,[31,32] and the individual voice laboratory standard methods. The lack of a standardized acoustic analysis obtained across laboratories represents a limitation of comparing such parameters in multicenter work. It may also be suggested that various results between different acoustic laryngological studies to some extent are caused by lack of such standardization of the analyses. At last, the control group comprised healthy mostly young subjects giving an age difference between the controls and the patients. It is possible that to include elder patients with nonlaryngological diseases as controls would have been a better approach as control conditions. The dysfunctional disease group has, however, to a large extent scored similar to the control group, and thus serves to validate the control group.

Jitter, shimmer, and NHR scores correlated closely. This is in accordance with the findings of findings of Ziwei and allied.[33] These parameters thus seem to reflect a common underlying entity. The parameters are, however, obtained by separate analysis of the data and thus add to the reliability of the data. Age of the patients may also be of importance as to acoustic analyses.[34,35] This has also been shown in the present study regarding jitter, shimmer, and NHR. Acoustic measurement absolute values were presently generally scored different among males and females which previously as also have been shown to be the case.[36,37] Variable age and gender did not remove significant results regarding jitter, shimmer, and MPT on diagnostic group measured by ANOVA analyses adjusted by age and gender used as covariates. Gender influenced the significant differences concerning the F0, and here separate analyses dependent on gender were conducted. Larger studies are needed in order to determine more conclusively the importance of age and gender as to acoustic analyses dependent on diagnosis.

A large variety of diseases affecting the larynx may influence the voice. To collapse diagnoses into broader groups are often needed, but challenging in order to analyze results like the present.[28,29] Cancer patients form one group as the etiology, symptoms and treatment is similar. The same is the case regarding symptoms from recurrent nerve palsy patients. As long as acoustic analyses measures physical symptoms it is to be expected that dysfunctional disease patients scores as one group alongside control-like scores. Benign laryngeal disorders that cause dysphonia by affecting the physical structure of the vocal folds also seem pertinent to look upon as a group.[38] To some extent this is also the case with laryngitis making it possible to place such patients in this group. Placement of specific diseased patients in collapsed groups may, however, be a matter of discussion, and so far no general guidelines have been agreed upon. With more patients included, discrepancies between more specific diseases could have been better studied.

The F0 values presently scored in particular differently between males and females.[39] We have furthermore shown that male cancer patients scored with lower frequency than the male controls. Regarding females, the controls scored with higher frequency than the recurrent palsy and the degenerative or inflammatory diseased female patients. To what extent these findings are gender-related or general must be determined by future investigations.

One major symptom of recurrent palsy is shortened phonation time per expiration while phonating with expected reduced MPT.[40] MPT was, however, not presently significantly decreased among the recurrent palsy patients compared to the controls. Jitter, shimmer and NHR values have presently been shown to be higher among recurrent palsy patients than at control conditions, as is previously supported regarding jitter values.[6] Recurrent palsy patients thus scored to some extent divergent to what we expected compared to control conditions regarding MPT. This has to be further studied.

Former cancer patients also scored systematically different than the controls regarding the acoustic analyses determined. This is as expected.[18] The degenerative and inflammatory group also showed pathological values relative to the control groups. This is in accordance with results published by Schindler and allied[6]. Inflammatory or degenerative disease patients also scored with more pathology than the controls. This is in line with Zhuge and allied[19] who determined that vocal polyps cause increased jitter.

Patients with dysfunctional diagnosis did not score different regarding acoustic analyses than the controls. The physical characterization of the voice by the measured parameters was thus as the controls. Acoustic analyses may thus contribute to finalizing functional diagnoses.

Presently, we have shown that VHI scores correlate with acoustic measures with about 10% common variance among all included patients. In particular, this was seen regarding jitter, shimmer, NHR complex, but mainly among the cancer and degenerative/inflammatory patients and primarily tied to jitter. We find it supported that the perceived voice handicap level is associated to physical disease of the vocal cords as is also supported by Wuyts and allied.[41] Other factors than the physical characteristics of the voice may be the important part in the recurrent palsy, dysfunctional as well as the control group when persons generate VHI scores. Thus, there seems not to be a strong general association between VHI scores and acoustic parameters in the groups without direct vocal cord disease as is supported by other investigators.[6,27] This is also supported by the fact that it is often low correlations shown between physical disease factors and quality of life scores.[42] There is a need to further study VHI versus acoustic scores at specific disease level, especially including more patients in order to study degenerative/inflammatory patients.

As shown in the present study at group levels acoustic voice analyses studied by specific laryngeal diseases reflect in particular if voice physical pathology is present or not. In addition to some extent the magnitude of such pathology is reflected. These analyses may therefore be important as proxy variables concerning potential treatment effects. This is presently especially the case with jitter, shimmer and NHR as supported by Gillespie and allied.[43] To study laryngeal patient acoustic analyses dependent on difference from controls further will be a future aim in order to study if the discrepancy power can be used at individual level. Between various patients presently acoustic analyses only seems to be most useful at group levels. If new studies are conducted in a multicenter fashion, one will know more exact yield of adding acoustic measurements to the diagnostic workup of individual laryngological patients.

CONCLUSIONS

We have shown among larynx disease patients that acoustic analysis may segregate between in particular patients as groups with laryngeal cancer, laryngeal degenerative/inflammatory disease and recurrent palsy, but not dysfunctional disease compared to control conditions. VHI scores correlate to acoustic scores among laryngeal cancer and laryngeal degenerative/inflammatory patients. Acoustic analyses hold the promise to be an importance measure when diagnosing and treating laryngological disease.

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