Dyspnea, with a focus on cardiovascular diseases:

A primary health care perspective

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I dedicate this to my beloved wife;
Sheyda,
and our two fantastic children;
Shilan and *Zanyar*

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ABSTRACT

Aim: The overall objective of our thesis is to describe, identify, and quantify the essential aspects of dyspnea both as a stand-alone symptom and as a symptom in patients with a special focus on cardiovascular diseases in the primary health care.

Introduction: Despite a high prevalence of dyspnea in the general population there is a small fraction of these individuals seeking medical advice in primary health care settings. A better understanding of this complex symptom of numerous chronic diseases requires more active research on dyspnea and suffering patients.

Methods: Paper I (n=20) was a qualitative study with a content analysis of diaries provided to patients with dyspnea. They were asked to write down their experiences with the symptom over seven consecutive days. In paper II (n=1058), a community based study, we analyzed data from the Vara-Skövde Cohort, revealing the association between self-rated health (SRH) and diastolic dysfunction. In study III (n=89), a cross sectional study, we examined various scales for measuring dyspnea [i.e., Visual Analogue Scale (VAS), Verbal Rating Scale (VRS), modified Medical Research Council (mMRC) dyspnea scale, and New York Heart Association (NYHA) classification scale] for quantifying dyspnea and relating it to patients' health-related quality of life (HRQoL) using the Short-Form 36 (SF-36) survey. In study IV, a longitudinal observational study, we studied a subpopulation from study III (patients with cardiovascular and pulmonary diseases) regarding changes in dyspnea and HRQoL after standard treatment.

Results: The qualitative analysis of dyspnea (I) showed that dyspneic patients despite a considerable reduced HRQoL, found relief in social support, leisure activities and coping strategies in addition to drug therapy. Study II showed that SRH and Nt-proBNP (N-terminal prohormone brain natriuretic peptide) were associated with diastolic dysfunction. The significant associations

remained intact even after simultaneous mutual adjustments for different factors, including age and sex. In study III, we confirmed that HRQoL was impaired in patients with dyspnea compared with HRQoL in the general population. The NYHA and mMRC scales were better correlated with each other than the VRS and VAS. Although the NYHA scale showed no correlation with different SF-36 domains, the mMRC scale showed a better correlation with 4 of the 8 domains. The VAS and VRS had a weak correlation with SF-36 domains. Study IV confirmed that the mMRC scale and VAS were appropriate measurement tools for assessing dyspnea in primary health care settings despite their different features. Changes in the different SF-36 domains were not observed after one year.

Conclusion: Dyspnea reduces patients' HRQoL, and the management of this condition should be both pharmacological and supportive, targeting patients' own abilities to cope with the symptom. We highlighted the role of SRH in association to diastolic dysfunction and confirmed the importance of Nt-proBNP as well. Assessing dyspnea in primary health care requires an appropriate and quick measurement instrument to evaluate dyspnea and an instrument to follow up patients with dyspnea. In addition, it is important to ask patients about how they experience their health state early in the assessment of dyspnea.

Implication: Utilizing diaries in assessing dyspnea gives yet another dimension in understanding the symptom and the suffering patients. SRH is useful in a targeted approach to the assessment of dyspnea. The VAS should be considered particularly for detecting long-term changes in dyspnea, while the mMRC scale is valuable for evaluating the impact of dyspnea on HRQoL.

Keywords: CVD, COPD, diastolic dysfunction, dyspnea, heart failure, HRQoL, mMRC, one-dimensional scales, primary health care, SF-36, SRH, VAS, VRS

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SAMMANFATTNING PÅ SVENSKA

Dyspné, med fokus på hjärt-kärlsjukdomar. Ett primärvårds perspektiv

Syfte: Det övergripande syftet med avhandlingen var att beskriva, identifiera och kvantifiera de viktigaste aspekterna av dyspné. Vi försökte ge riktlinjer för bedömning, mätning och hantering av dyspné, med särskilt fokus på hjärt-kärlsjukdomar och patienter i primärvården.

Bakgrund*:* Dyspné eller andnöd är ett svårdefinierat symtom som patienterna kan uttrycka på olika sätt som kortandning, tryck över bröstet, lufthunger eller orkeslöshet vid ansträngning etc. American Thoracic Society definierar dyspné som en subjektiv upplevelse av andnöd som består av kvalitativt distinkta sensationer med varierande intensitet. Till följd av sin komplexa och mångsidiga karaktär orsakar dyspné inte bara nedsatt funktionskapacitet och mycket obehag hos patienten men också social isolering och dålig livskvalitet. Många patienter har en känd bakomliggande orsak men flertalet kommer med nydebuterad dyspné utan tidigare diagnos. Den komplicerade karaktären av dyspné som ett symtom speglar tre mätvariabler som upplevs av patienten som: 1) intensiteten och varaktigheten av symptom; 2) upplevt obehag, och 3) effekten av dyspné på vardagen och livskvaliteten. Livskvalitet är ett flerdimensionellt begrepp med filosofiska, sociologiska, och ekonomiska aspekter. I ett bra liv, är frågan om hälsa en central fråga. Därför är hälsotillstånd ytterligare en dimension av livskvalitet, benämnd hälsorelaterad livskvalitet som kan mätas bland annat av short form 36 (SF-36), ett frågeformulär med 11 frågor och 8 dimensioner vilka täcker olika fysiska, psykiska, och sociala kvaliteter. Det är fastställt att skattning av andfåddhet genom att mäta symptomintensiteten möjliggör en bättre uppföljning av behandlingseffekt samt prognostiska upplysningar. Emellertid saknas det en så kallad guldstandard för långtidsuppföljning av patienters andfåddhet.

Tidigare arbeten är oftast gjorda i slutenvårdsmiljö och riktad mot grundsjukdomen bakom andfåddheten, exempelvis: hjärtsvikt, kronisk obstruktiv lungsjukdom (KOL) och astma. Trots den höga förekomsten av dyspné i befolkningen, beräknas andelen av konsultationer för dyspné vara mellan 0,90 % till 2,50 %.

Det finns behov av studier som med klar frågeställning och lämpligt mätinstrument evaluerar olika sätt att förbättra den diagnostiska processen vid utvärdering av dyspné och förbättra livskvaliteten för patienter som lider av andfåddhet. I denna avhandling har vi haft för avsikt att studera andfåddhet från patientens perspektiv men också analysera patientens hälsotillstånd och livskvalitet med olika kliniska mått för att se hur patientens livskvalitet är påverkad och hur den kan följas. Det finns kunskapsluckor om utredning,

omhändertagande, mätning och livskvalitet hos patienter med dyspné i primärvården på grund av begränsade antal studier av dyspnea i primärvårdssammanhang. I vår avhandling, med hjälp av både kvalitativa och kvantitativa metoder, genomförde vi undersökningar för att ytterligare utvärdera dyspné i primärvården. I vår första studie analyserade vi hur dyspné påverkar det dagliga livet för patienter. I vår andra studie analyserade vi förhållandet mellan självskattad hälsa (SRH) och diastolisk dysfunktion (störning i hjärtats fyllnadsfas). I studier III och IV, jämförde vi olika skalor för att mäta dyspné i samband med hälsorelaterad livskvalitet hos patienter med dyspné, och vi klargjorde etiologi och underliggande sjukdomar relaterade till dyspné.

Metod: *Studie I, Kvalitativ studie med induktiv innehållsanalys*
Frågeställningen var hur patienter som lider av andfåddhet upplever sin vardag och hur skattar man symtomgraden med hjälp av en visuell analog skala [Visual Analogue Scale (VAS)] genom att markera på VAS skalan som är graderad 0 till 100 mm. Urvalsstorleken var 20 personer. Studien gjordes under 7 dagar och patienterna skrev dagligen om sina upplevelser med andfåddheten i en dagbok samtidigt som de markerade på VAS skalan hur mycket andfåddhet de hade.

Studie II, En populationsbaserad tvärsnittsstudie
Vi undersökte sambandet mellan Självskattad hälsa (SRH), hjärtsviktmarkören Nt-proBNP, och diastolisk dysfunktion, med data från en stor befolkningsbaserad studie (Vara-Skövde Kohorten).

Studie III, En tvärsnittsstudie
Studien har en beskrivande design som genomfördes på en vårdcentral i Västsverige. Data erhölls som patientrapporterade utfallsmått baserat på fyra endimensionella skalor [New York Heart Association (NYHA) scale, modified Medical Research Council (mMRC) scale, Verbal Rate scale (VRS), samt VAS] för att mäta dyspné relaterat till olika dimensioner av frågeformuläret Short Form 36 (SF-36). Vi ville undersöka respektive skalas potential till korrekt andfåddhetsmätning i förhållande till patienters hälsorelaterade livskvalitet.

Studie IV, Longitudinell observationsstudie
Studien var en longitudinell studie som var designad för att följa upp en delpopulation av de patienter som hade hjärt-kärlsjukdomar respektive lungsjukdomar i studie III. Uppföljningen utfördes efter ett år och de instrument som nämndes för studie III användes igen ett år senare för att registrera förändringar i patienters dyspné relaterad till deras livskvalitet.

Resultat: Den kvalitativa analysen av dyspné *(I)* visade att patienter med betydande andnöd, hade nedsatt fysisk förmåga, betydande psykisk ohälsa samt social isolering men fann ändå lättnad i fritidsaktiviteter och socialt stöd,

och de utvecklade anpassningsstrategier. *Studie II* visade ett statistiskt signifikant samband mellan både SRH och Nt-proBNP (N-terminal B-type natriuretic peptide) med diastolisk dysfunktion. Signifikansen förblev intakt även efter justering för andra riskfaktorer, ålder och kön. I *studie III* bekräftades att hälsorelaterad livskvalitet var nedsatt hos patienter med dyspné jämfört med den allmänna befolkningen. NYHA och mMRC var bättre korrelerade med varandra än VRS och VAS. NYHA visade ingen korrelation till olika SF-36 dimensioner, men mMRC visade en bättre korrelation med fyra av åtta dimensioner av SF-36. *Studie IV* bekräftade att mMRC är lämpliga mått för skattning av grad av dyspné relaterad till livskvalitet medan VAS visade en klar förbättring hos patienter med hjärtkärlsjukdom efter standardbehandling. Det senare talar för lämpligheten av VAS i uppföljning av dyspné hos patienter med hjärtkärlsjukdomar. Inga dimensioner av SF-36 var signifikant ändrat jämfört med året innan.

Konklusion: Dyspné har negativ inverkan på livskvaliteten hos drabbade patienter. Vid sidan om den farmakologiska behandlingen har patienterna nytta av social support, fysisk aktivitet och egen livsanpassning. Vi betonar betydelsen av att mäta självskattad hälsa, liksom Nt-proBNP som associativa faktorer till diastolisk dysfunktion. Det betyder också att störningar i hjärtats fyllnadsfas trots allt upplevs av patienten fast det är känt för att vara symtomslös. Vidare anser vi att bedömning av dyspné i primärvården kräver ett lämpligt och lättanvänt mätinstrument som kan användas både i diagnostik och i uppföljning av patienter med dyspné.

Implikation: Att använda dagböcker ger bättre förståelse av patienterna och deras symtom. SRH är en användbar egenskap som underlättar en målinriktad strategi för utredningen av dyspné. VAS bör övervägas särskilt för att upptäcka långsiktiga förändringar av andnöd medan mMRC är värdefull i utvärderingen av symtomets intensitet med god korrelation till patientens livskvalitet.

Nyckelord: CVD, KOL, diastolisk dysfunktion, dyspné, endimensionell skala, HRQoL, mMRC, primärvården, SRH, VAS

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LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Ahmadi, NS, Lindblad, U, Månsson, J, Hildingh, C. Breathlessness in everyday life from a patient perspective: a qualitative study using diaries. **Palliat Support Care. 2014 Jun; 12(3):189-94.**

II. Ahmadi, NS, Bennet, L, Larsson, CA, Andersson, S, Månsson, J, Lindblad, U. Clinical characteristics of asymptomatic left ventricular diastolic dysfunction and its association with self-rated health and N-terminal B-type natriuretic peptide: a cross-sectional study. **ESC Heart Failure. September 2016, Volume 3, Pages 205-211**

III. Ahmadi, NS, Lindblad, U, Månsson, J. Impairment of health-related quality of life in dyspnea, assessed using multiple severity scales. **Submitted.**

IV. Ahmadi, NS, Lindblad, U, Månsson, J. Dyspnea, symptom intensity and impact on health-related quality of life in patients with cardiovascular or pulmonary diseases – a community based longitudinal study. **Submitted.**

CONTENT

ABBREVIATIONS

ATS	American Thoracic Society
BDI	Baseline Dyspnea Index
BMI	Body Mass Index
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
DD-PSF	Diastolic Dysfunction with Preserved Systolic Function
QoL	Quality of Life
HRQoL	Health-Related Quality of Life
LVDD	Left Ventricular Diastolic Dysfunction
mMRC	modified Medical Research Council
NYHA	New York Heart Association
Nt-proBNP	N-terminal B-type natriuretic peptide
OR	Odds Ratio
PROM	Patient-Reported Outcome Measure
SF-36	Short-Form 36 Health Survey
SRH	Self-Rated Health
TDI	Transition Dyspnea Index
VAS	Visual Analogue Scale
VRS	Verbal Rating Scale

1 INTRODUCTION

Assessing dyspnea is like solving a puzzle. One must have a picture in mind before one begins solving the problem, but the best process for coming to the right conclusions is still unclear. Dyspnea, or breathlessness, may be the first sign of a serious disease or the end-result of another one. The symptom is frequent, complex, and very unpleasant for suffering patients.

There is controversy regarding the proper definition of dyspnea despite extensive information clarifying this condition from the late 1990s. This emphasizes the complexity of this important symptom and the fact that it is not completely understood. With this perspective in mind, I started my research on this fascinating subject in 2009. My background as both a cardiologist and general practitioner was an advantage in meeting with patients seeking advice for dyspnea in the primary health care setting. I could perform echocardiographic examinations with my portable echocardiography equipment almost immediately as part of the assessment process, which gave new insight into examining the status of the whole heart, something that is nearly impossible to do using only a stethoscope. The complexity of dyspnea awoke my curiosity to study the subject further. In recent years, there has been a renaissance in research on dyspnea; however, the need for more studies on dyspnea in primary health care is apparent.

2 BACKGROUND

2.1 Definition of Dyspnea

The Latin term *dyspnea* originates from the Greek *dyspnoia,* from *dyspnoos*, which means "disordered breathing" (1). However, dysfunctional breathing is a term that refers to a category of breathing disorders in patients with perceived dyspnea in the absence of a specifically identifiable respiratory disease (2,3). We use the word dyspnea here to describe the subjective symptom of "breathlessness," "shortness of breath" or "air hunger" perceived by patients (4).

A consensus statement from the American Thoracic Society (ATS) in 1999 defines dyspnea in the following way: "Dyspnea is a term used to characterize a subjective experience of breathing discomfort that is comprised of qualitatively distinct sensations that vary in intensity" (5). From a clinical point of view it is important to differentiate between acute and chronic dyspnea. Acute dyspnea develops over hours to days, whereas chronic dyspnea remains for more than several weeks or months (6).

2.2 Physiology

In the 2012 update of its consensus statement, the ATS added:

"Different physiological, psychological, social, and environmental factors interact and drive the experience of dyspnea" (7), which may induce secondary physiological and behavioral responses (8).

The conceptual framework for our understanding of dyspnea, based on a neurobiological model, includes complex interactions between a variety of respiratory stimuli associated with certain sensory receptors (9). The stimulation of sensory receptors reaches the CNS via afferent impulses, and processing and integration occur in the sensory cortex. The motor cortex engages the efferent pathways leading back to the phrenic nerve and the thoracic muscles, which modulate breathing patterns, completing the circuit. Any disturbances in this system results in the subjective feeling of dyspnea. Examples of such disturbances include the stimulation of carotid and aortic bodies by hypoxia and medullary chemoreceptors by hypercapnia or acidosis. Dyspnea can also be induced by pulmonary congestion, which activates pulmonary C-fibers, by airway collapse, which stimulates bronchial C-fibers, and by disturbances in the limbic system, which is highly affected by emotions (10,11). The involvement of different afferent mechanisms explains the

multidimensionality of dyspnea (12,13). The neurosensory processing of dyspnea has similarities to the processing pathway for nociception (7), which adds to the complexity of the subjective perception of dyspnea. New neuroimaging techniques as Positron emission tomography (PET) or functional magnetic resonance imaging (fMRI) have provided insight into the cerebral mapping of the perception of dyspnea and the corticolimbic circuitry (14). In the light of this new knowledge, one can understand how and why dyspnea leads to fear, anxiety, and anger, and the multidimensionality of dyspnea becomes evident. New instruments to measure dyspnea continue to be developed, and the necessity of clinically measuring dyspnea is more discussed than ever (15). This new understanding of the physiology of dyspnea opens a window of opportunity to redefine the epidemiology of dyspnea, and the development of new methods for measuring this condition is an excellent way to find patients with dyspnea in the general population. Similar to hypertension in the general population, the number of people suffering from dyspnea who seek medical advice is just a fraction of the total number who suffer from dyspnea. It is just the tip of the iceberg.

2.3 Epidemiology

Dyspnea is a distressing sensation that increases in the general population with age. The prevalence of breathlessness among the elderly has been reported to be between 20 and 45% (16,17). Despite this fact, few studies have addressed this important issue in primary health care. Frese et al. declared that “data from the primary health care setting on the epidemiology, management, and underlying causes of dyspnea have seldom been published”, and in his extensive survey in a European general population (n=7855), he found that approximately 2.5% of patients sought medical advice for dyspnea. The average age of those seeking advice was 65 years, and the male to female ratio was almost 1:1; half of these patients sought medical advice for previously unknown dyspnea (18).

In a major literature review (19) examining 9,323 studies (1950-2012), the author found only one study (20) investigating the underlying causes of dyspnea in the general population. Of the 129 subjects with dyspnea that were studied, 68 (53%) had signs of lung disease, 27 (21%) had heart disease, 20 (16%) were obese without other causes of dyspnea and five (4%) were in generally poor physical condition. Twelve percent had none of the potential causes of dyspnea mentioned above (20).

2.4 Aetiology

Chronic dyspnea is the most prominent symptom in cardiovascular (21,22) and pulmonary diseases (23,24). The underlying causes are primarily cardiopulmonary diseases such as heart failure, ischemic heart disease *(*IHD), asthma and chronic obstructive pulmonary disease (COPD). However, obesity, anxiety, anemia, neuromuscular diseases and advanced cancer can also cause breathlessness, and anxiety, depression, and neuromuscular diseases have been specifically found to be associated with dyspnea (25,26). Therefore, the assessment of dyspnea can occur along different clinical pathways depending on the suspected underlying aetiology. Currently, measuring dyspnea is a mandatory part of patient assessments (27). According to standard guidelines, symptoms and lung function should be monitored to manage patients with COPD and asthma (28). Dyspnea is the most frequent symptom prior to the hospitalization or readmission of patients with major cardiopulmonary diseases (29,30). Dyspnea, as a primary symptom in many clinical situations, could be an indication of a chronic or acute underlying disease (31). One important underlying condition is heart failure, which explains more than 10% of the prevalence of dyspnea among the elderly (32). Breathlessness is difficult to quantify due to the subjectivity of the symptom and, in that respect, it may be compared to pain or fatigue (33). Understanding dyspnea from a patient perspective is, however, necessary due to the reasons mentioned above.

2.5 Assessment of dyspnea in primary health care

Despite the high prevalence of dyspnea in the general population, consultations for dyspnea as a stand-alone symptom are rarely registered. The prevalence of dyspnea as a reason for seeking medical advice in primary health care ranges from 0.90 to 2.50 % (34). Furthermore, Viniol A et al. noticed in their systemic review of dyspnea studies that there is a marked lack of evidence relating to its prevalence, aetiology and prognosis in general practice, which adds to the dubiousness in diagnoses and assessments of dyspnea in primary health care. Dyspnea, as a component of advanced diseases, is common in primary health care (35). Whether dyspnea should be considered a stand-alone phenomenon or as part of an underlying disease is an ongoing discussion.

The evaluation of dyspneic patient begins with their history and a physical examination (H&P). A thorough recording of their history is a necessary part of the initial assessment of dyspnea that reveals its onset, duration, and severity. Patients should be asked about the occurrence of dyspnea at rest and during physical activity, and asking questions about their social history, working environment, tobacco use and medication, add important information.

Basic laboratory studies is the next step in evaluation of dyspnea (36). Electrocardiograms (ECGs), chest X-rays, and spirometry should be the first line of further investigation of patients with dyspnea in primary health care. In addition to clinical signs, such as effort intolerance and dyspnea, echocardiography and the detection of elevated levels of the N-terminal B-type natriuretic peptide (Nt-proBNP) have been used as diagnostic tools for assessing patients with heart failure (37). One approach for identifying risk factors is the use of different health metrics. According to current procedures, patients should be admitted to secondary care for echocardiographic examination when elevated Nt-proBNP levels indicate possible heart failure. Pratter et al., in their algorithmic approach to assessing chronic dyspnea, suggest a diagnostic process based on several stages, concluding that: "patients presenting with dyspnea have a broad range of underlying diagnoses" and advocating for a broad multidisciplinary approach (38).

2.5.1 Health-related quality of life and measurements of dyspnea

The complex nature of dyspnea as a symptom reflects three different primary clinical outcomes experienced by the patient: 1, the intensity and duration of the symptom; 2, perceived unpleasantness and discomfort (15); and 3, the impact dyspnea has on everyday life and the degree to which it reduces quality of life (QoL) (7). QoL is a multidimensional concept with philosophical (39), sociological (40), and economic (41) aspects. However, QoL is mostly a factor of individual perception (42). In a good life, the question of health is a central issue. Therefore, health status is yet another dimension of QoL, referred to as health-related quality of life (HRQoL) (43). In scientific research, HRQoL refers to the physical, emotional, and social well-being of a patient (44) according to the WHO's (World Health Organization) definition of health. Most studies assessing health status use a generic HRQoL instrument, with the 36-Item Short-Form Health Survey (SF-36) being the one most commonly used (45). Therefore, the inclusion of patient-reported dyspnea measurements (PROs) has been suggested, which would provide a measure of the health status as reported directly by the patients (46, 47). Measurements of dyspnea have been debated since the 1960s, and the paradigm was that it was impossible to measure the various aspects of dyspnea. However, the first attempts were made in the 1980s after acknowledging that part of the symptom is a sensory experience (48). Several reliable scales with a high validity exist that measure these outcomes, and there are various scales for measuring dyspnea. One-dimensional scales that measure different qualities of dyspnea, such as its intensity and severity [i.e., Verbal Rating Scale (VRS) (49), and Visual Analogue Scale (VAS)] (50) and its impact on physical activity [i.e., modified Medical Research Council (mMRC) scale] (51) are most frequently used. A systematic review of dyspnea conducted by Dorman and colleagues showed

that these instruments could be classified according to the domain of dyspnea they measure, such as symptom severity [(e.g., VAS, Numeric Rating Scale (NRS)] or impact on functionality [(e.g., mMRC, Baseline Dyspnea Index (BDI) or Transition Dyspnea Index (TDI)] (52-54). Similar to pain, dyspnea is also a key factor underlying an individual's HRQoL (35) and long-term mortality (55). New York Heart Association (NYHA) Functional Classifications are a recognized tool for the assessment of dyspnea and fatigue in heart-related diseases (56). The classification of dyspnea scales as one-dimensional (e.g., VAS, MRC, Borg scale) or multidimensional (e.g., BDI/TDI) was first suggested by Mahler et al. (57-59). Another researcher focused on the question of the symptom- (e.g., VAS, VRS) or disease-specificity (e.g., mMRC, BDI/TDI) of the scales. However, with the lack of a gold standard, a combination of both one-dimensional and multidimensional instruments in the clinical assessment of dyspnea has been suggested (27).

Regardless of the classification scale used, it is now established that monitoring dyspnea by measuring symptom intensity in the early stage of the assessment process enables an estimate of improvements in symptoms. It also reduces the risk of the underlying condition deteriorating by providing therapeutic control, which may enhance HRQoL among patients (60). A variety of disease-specific questionnaires and multidimensional instruments are often employed for exploring HRQoL among patients with dyspnea (61, 62). In the latter case, despite the psychometric qualities of the SF-36, few studies have applied the SF-36 to the study of dyspnea (63). However, the need for a standardized approach to measure dyspnea in clinical trials has been discussed (64), and it is an equally important matter to discuss in clinical settings, especially in primary health care.

2.5.2 Long-term changes in dyspnea

Monitoring dyspnea over long time periods (65, 66) is important to determine how patients respond to therapy received to alleviate the negative impact of dyspnea on HRQoL (67). However, the lack of a gold standard for such monitoring has been previously reported (68). Despite recommendations to use the mMRC scale (69), its effectiveness for long-term follow-up has been questioned (65). How different aetiologies can lead to differences in how fast dyspnea worsens is unclear, and whether the worsening of dyspnea is a result of impaired lung function over time is also debated in the literature (70).

However, our knowledge about the prevalence and underlying aetiology of dyspnea is mostly from studies done in secondary care clinics or dyspnea laboratories. Empirical evidence about the epidemiology, aetiology, prognosis, HRQoL, and symptom evaluation from studies of dyspneic patients in primary

care settings is very limited (34). In the current thesis, using both qualitative and quantitative methods, we conducted investigations to further evaluate the symptoms of dyspnea in primary health care settings. In our first study, we analyzed how dyspnea impacted the day-to-day lives of patients. In our second study, we analyzed the relationship between answers to self-rated health (SRH) questions and diastolic dysfunction. In studies III and IV, we compared different scales for measuring dyspnea related to HRQoL in patients with dyspnea, and we further clarified the aetiology and underlying diseases related to dyspnea.

3 AIM

3.1 Overall objectives

The overall objective of our thesis was to describe, identify, and quantify the essential aspects of dyspnea. We sought to provide guidelines for the assessment, measurement, and management of dyspnea, with a special focus on cardiovascular diseases and patients in primary health care settings.

3.2 Specific objectives

I. To explore how patients, describe their daily lives with breathlessness.

II. To investigate the association between SRH and diastolic dysfunction with preserved systolic function, accounting for the role of Nt-proBNP, and to examine the clinical characteristics of subjects with diastolic dysfunction in the general population.

III. To identify an appropriate scale to measure dyspnea as a stand-alone symptom, in a manner that reflects the multidimensionality of the symptom, in patients complaining of dyspnea in primary health care settings.

IV. To determine one-year changes in dyspnea and the impact it has on HRQoL in patients with cardiac or respiratory diseases.

4 METHODS

4.1 The site of the study

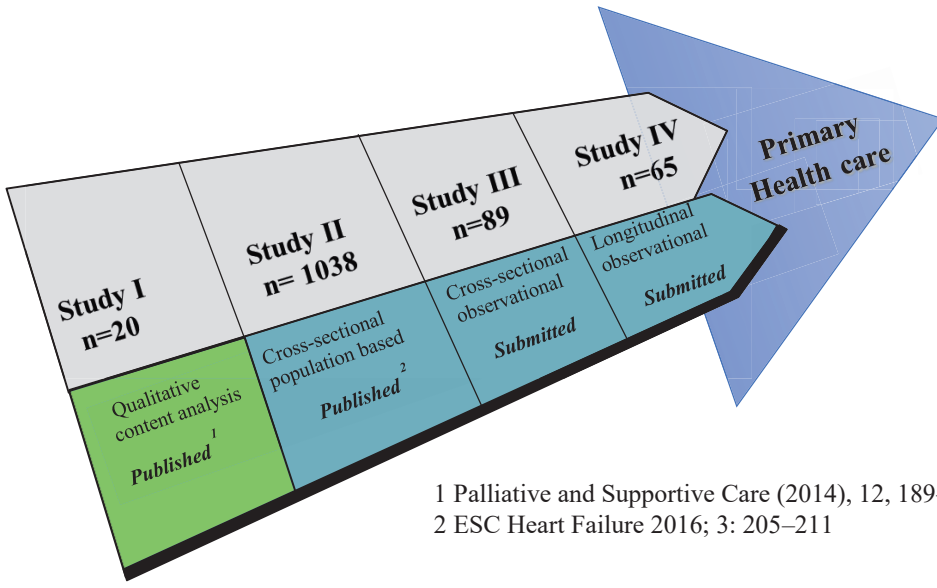
The primary health care centre where studies I, III and IV were conducted is located in the rural town of Henån on the island of Orust, which is the largest island on the West Coast of Sweden. The Orust municipality has approximately 15,000 (2013-12-31) inhabitants, and the primary health care centre serves approximately 8,800 inhabitants living in the Orust community.

Study II included data from a population survey conducted in 2002–2003 in Vara, a small municipality with 16 000 inhabitants in a rural area of south-western Sweden.

4.2 Study designs

Participants in all studies underwent a physical examination, provided informed consent, and completed the survey questionnaires. Standard blood

Figure 1. The study design and the number of participants (I-IV)



1 Palliative and Supportive Care (2014), 12, 189–194.
2 ESC Heart Failure 2016; 3: 205–211

samples were taken from all participants, and spirometric and echocardiographic examinations were performed as part of the studies in selected and predefined cases. The study design and populations are briefly summarized in Figure 1.

4.2.1 (I) Qualitative study with inductive content analysis

The main research question was how was to determine how patients suffering from breathlessness experience their everyday life and how they rate their symptoms on a daily basis using VAS.

The sample size was 20 individuals.

4.2.2 (II) Cross-sectional population-based study

To explore the association between SRH and Nt-proBNP, respectively, with diastolic dysfunction, we utilized data from the baseline visit of the Vara-Skövde Cohort (71).

4.2.3 (III) Cross-sectional observational study

The third study was a cross-sectional study with a descriptive and correlational design and was conducted in the primary health care unit of a single health centre. Data were obtained as patient-reported outcome measures based on four one-dimensional scales for measuring dyspnea based on similar constructs and the SF-36 questionnaire. The information for internal consistency and reliability, and correlation coefficients within and between items were calculated. One important issue was the prevalence of dyspnea as the reason for seeking consultation and the underlying diseases.

4.2.4 (IV) Longitudinal observational study

The study was a longitudinal study with a descriptive and correlational design. We conducted the study on a subpopulation of the participants in study III. Patients with cardiovascular and pulmonary diseases were selected and followed up during one year. Changes in dyspnea intensity and the impacts on HRQoL were determined at the end of study period.

4.3 Study populations

4.3.1 Study I

Twenty individuals were selected on a voluntary basis from patients visiting doctors or specialist nurses to manage their breathlessness. The inclusion criteria were the presentation of breathlessness regardless of the underlying disease and that the patient was an adult. Patients with a life-threatening illness, severe neuralgic disorder, dementia or pregnancy were excluded.

4.3.2 Study II

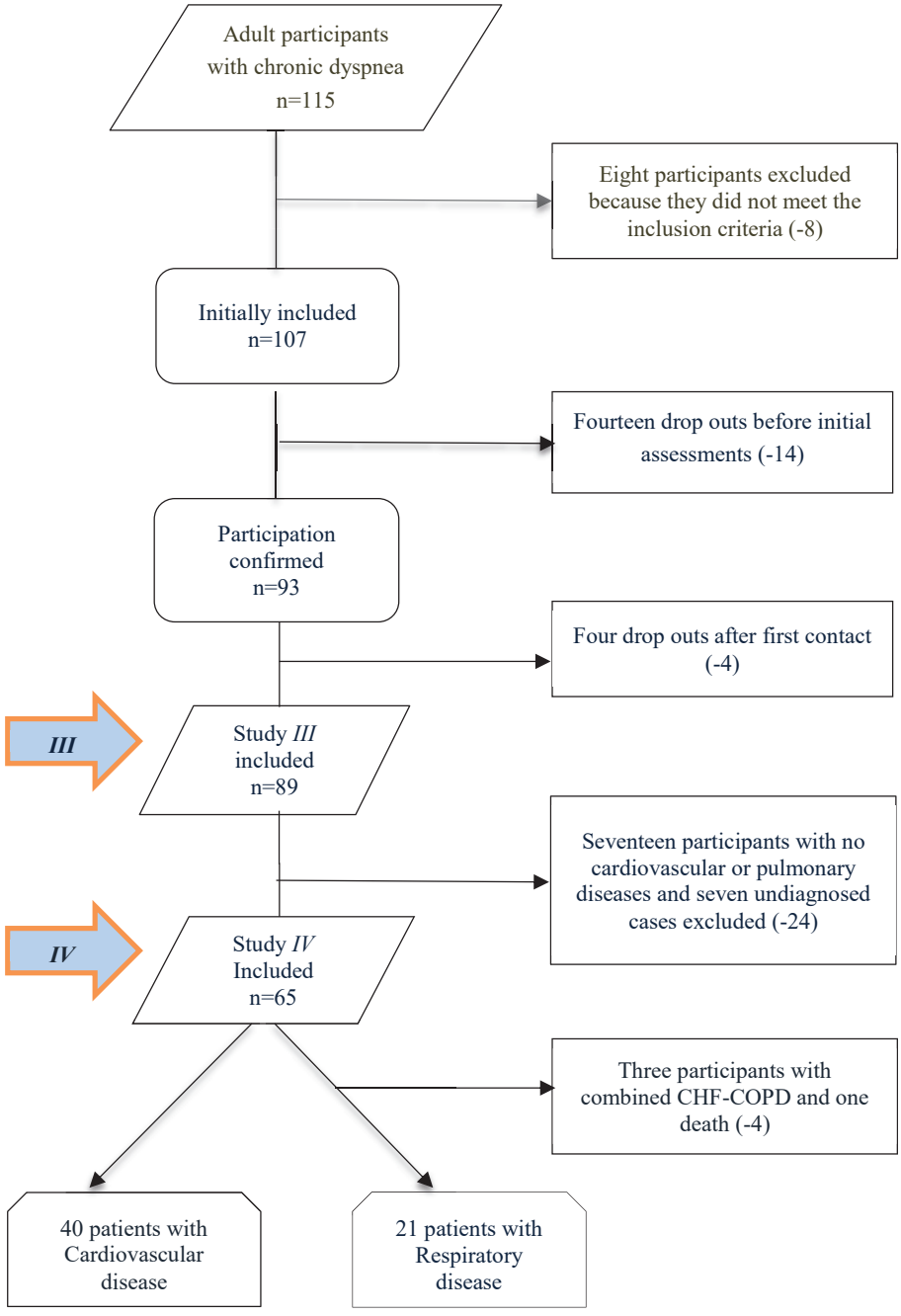
Vara is a small municipality with 16,000 inhabitants in a rural area of south-western Sweden. Between 2002-2004, a random sample of 1,811 participants aged 30-74 years were surveyed for cardiovascular risk factors and impaired glucose metabolism (72). At a second visit, 1,058 participants were consecutively examined using conventional echocardiography and tissue velocity imaging (71). However, 20 participants could not fully participate due to various reasons that have been reported in detail previously (73). Thus, the presence or absence of diastolic dysfunction was determined in 1,038 participants: 500 men and 538 women (90% of those invited for the echo-Doppler investigation).

4.3.3 Study III & IV

Patients were sampled from the 8800 listed patients of the Capio Orust Health Centre in Orust, a rural community located in western Sweden. The inclusion criteria for enrolment in the study were that the patient was an adult (≥18 years) with dyspnea without a confirmed aetiology and that had lasted for at least six weeks as the main complaint prior to consultation. The exclusion criteria were pregnancy, dementia, psychosis, and severe neurological disorders. Patients were recruited on voluntary basis through the medical staff of the health centre.

During 2013-2014, we identified 115 patients with dyspnea. After exclusion and dropouts, 89 patients were included in study III. Figure 2 provides an overview of the different phases of the patient selection process and the final participation in the study. For study IV, we included only patients with suspected cardiovascular diseases from study III, and excluded patients with diagnoses of psychiatric disorders, according to our research protocol.

Figure 2. Flowchart of eligibility and participants included in the study III and IV



4.4 Data collection

4.4.1 Study I

We chose diaries as data collection tools because diaries have not been explored as frequently as ordinary interviews in the setting we studied. The participants were asked to write down all their experiences with their perceived breathlessness during the day and answer two questions over seven consecutive days according to the form displayed on Table 1. All participants were also asked to declare their health state related to their breathlessness during the day once a day based on the VAS.

Table 1. The model of the diary

The Quantitative part	The Qualitative part
VAS	**The questions**
Please put a cross on the line at the point that best describes how you felt today: not well very well	1. Please state if you have experienced breathlessness during the past 24 hours or felt unwell for some reason. Has your sleep been affected by your breathlessness? Please describe how you manage everyday life (work/leisure) despite your breathlessness. 2. Did you talk to any other people during the day about your health problems or did someone give you advice or help, for example, your family, friends, telephone based care, nurses, pharmacies or alternative medical practitioner?

4.4.2 Study II

All participants were examined via a 12-lead standard ECG. Their history was collected via questionnaire. Nt-proBNP concentrations were analyzed using standard methods. General SRH was defined based on five alternative answers described earlier, and the questionnaire was completed at the clinic with nurses providing assistance when needed.

All participants were examined via echo-Doppler examination performed by a senior cardiologist.

4.4.3 Study III & IV

For data collection, we used a booklet that included general questions about the patient's family situation (married or single), employment status (retired, active or disability pension), smoking habit (yes or no), comorbidities, and medications. The booklet also contained basic demographic questions, the four dyspnea measurement tools, and the SF-36.

For study III, data were obtained from patients who were assessed once using four one-dimensional scales for measuring dyspnea based on similar constructs and the SF-36 questionnaire. The data were analyzed for internal consistency and reliability, and correlation coefficients within and between items were calculated.

We planned three follow-up times after the initial contact. The first was 4-6 week after inclusion, the second was after 6 months and the last was after 12 months. Prior to the last consultation we provided the booklet containing the four one-dimensional scales and the SF-36 questionnaire to participants.

4.5 Patient reported outcome measures

4.5.1 Diaries (I)

Diaries are an accepted method of data collection in many different qualitative surveys (74). Unstructured diaries designed as open-ended questions give the participant the possibility to provide information without being precise in recalling events (75). The participants had the opportunity to write freely about their daily experiences with dyspnea over seven consecutive days, and by the end of observation period, they had produced brief narratives. To analyze the text, we followed the steps for analyzing qualitative data via content analysis described by Graneheim and Lundmann (76). The diaries were first read

through repeatedly in order to get a feeling for the overall context. Sentences that were relevant to the issue were then selected, and meaning-bearing units were identified, coded and categorized.

4.5.2 Self-Rated Health (II)

Self-rated health (SRH) or self-assessed health is a legitimate and recognized survey-based measure of health and has been used in medical research since the early 1970s when Maddox and Ware began their pioneering work studying measures of general health perception (77,78). Participants assessed their health via a single question, which was expressed in the form of: "in general, would you say that your health is" followed by five alternatives answers (excellent = 1, good = 2, fair = 3, poor = 4, very poor = 5). The validity of SRH has been supported by several studies (79,80), and Lundberg and Manderbacka found an excellent overall reliability of SRH in a Scandinavian study in 1996 (81). With these facts in mind and considering the simplicity of using a single question, SRH is an appropriate method for measuring health in all its dimensions.

4.5.3 Visual Analogue Scale (III & IV)

At baseline, we used a horizontal (100 mm) Visual Analogue Scale (VAS) scale, with "not breathless at all" marked at zero and "extremely breathless" marked at 100 mm. The person indicated their level of dyspnea by marking on the horizontal line between the two extremes (82).

4.5.4 Verbal Rating Scale (III & IV)

The Verbal Rating Scale was designed as a four-point Likert scale indicating four different levels of breathlessness: "No breathlessness," "Slightly," "Moderately" and "Severe breathlessness" (83).

4.5.5 Modified Medical Research Council dyspnea scale (III & IV)

The questions on the mMRC dyspnea scale describe five grades of dyspnea: "dyspnea only with strenuous exercise" (grade 0 or normal), "dyspnea when hurrying on the level or up a slight hill" (grade 1), "dyspnea when walking at own pace on the level" (grade 2), "dyspnea when walking 100 yards or for a few minutes" (grade 3), and "dyspnea at rest" (grade 4) (84,85).

4.5.6 New York Heart Association classification scale (III & IV)

The NYHA classification scale is used for assessing heart failure but has properties similar to an ordinal scale in rating dyspnea, and it shows the impact of breathlessness on patients with heart failure in order to classify the severity of cardiac decompensation in relation to physical activity. The different stages are as follows: Grade I: "No limitation in ordinary physical activity," grade II: "Mild dyspnea, slight limitation during ordinary activity", grade III: "Marked limitation of physical activity due to dyspnea even during less-than-ordinary activity", grade IV: "Experience symptoms even while at rest" (86). We have used the term "heart failure" instead of "congestive heart failure" according to the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) (87). All four one-dimensional scales are displayed in Appendix 1.

4.5.7 SF-36 (III & IV)

The SF-36, (displayed in Appendix 29), is an established health survey that is also self-assessed but addresses several dimensions of mental and physical health. The questionnaire has 36 items, which fall into eight different domains of health perception related to the disease or symptom in question (88). The SF-36 has already been validated for the general Swedish population in several controlled studies (89-91). The SF-36 has a high predictive value for a variety of chronic diseases (92-95). The eight domains of the SF-36 reflect the physical, emotional and mental health of the subject. The domains are physical functioning (PF), role limitations (RP) due to physical problems, bodily pain (BP), general health (GH) perceptions, vitality (VT), social functioning (SF), role limitations due to emotional problems (RE), and mental health (MH).

4.6 Advanced Diagnostic Equipment

4.6.1 Echocardiography

All participants in study II were examined via echo-Doppler scanning performed by the same senior cardiologist using a Vivid S5 GE VingMed Ultrasound (U.S.A.) operating with a 3.5-MHz probe. The echocardiography data were stored in the Echo Pac System for playback, analysis, and measurement. Measurements used for calculations of left ventricular function were obtained based on the Guidelines of the European Society of Echocardiography (96).

Participants in studies III and IV were either examined via echo-Doppler scanning performed by the researcher (N.S.A.) using a portable Vivid GE VingMed Ultrasound or were referred to the clinical physiological department of the local hospital for echo-Doppler examination.

4.6.2 Spirometry

Spirometry was performed locally using computer-based equipment (Welch Allyn, SpiroPerfect™ PC-Based Spirometer ECCS/Zapletal). Diagnoses of airflow obstruction were made for patients with forced expiratory volume in 1 second (FEV1)/forced vital capacity (FVC) ratios of less than 0.7 (i.e., 70%) and FEV1 values less than 80% of the predicted value (97). Diagnoses of asthma were confirmed if a postbronchodilator test showed at least a 12% improvement in FEV1 (98). Asthma and COPD were considered if obstructive patterns where found in the spirometric analyses, whereas interstitial lung disease (ILD) was considered if the total pulmonary capacity was decreased (6).

4.7 Statistics

4.7.1 Study II

Descriptive data were presented as the mean ± 1 standard deviation (SD) and/or median (min;max) for continuous variables and as numbers (n) and percentages (%) for categorical variables. ANOVAs and Student's t-tests were used to evaluate the mean differences between groups for continuous variables. Median and interquartile values were used to describe Nt-proBNP concentrations, and the p-values were computed using Mann-Whitney U tests. A binary logistic regression analysis was used to analyze the associations between DD-PSF, risk factors and comorbidities, and results were expressed as odds ratios (ORs) with 95% confidence intervals (CI)

4.7.2 Study III & IV

Statistical analyses were performed using the Statistical Package Software for the Social Sciences, SPSS version 21.0, (SPSS Inc., IBM, Chicago USA). For all statistical tests, alpha was set at 0.05, and all tests were 2-tailed. Within-subject Spearman correlation coefficients and their corresponding p-values (95% CIs) were calculated. Prior to data collection, a required sample size of approximately 44 participants was determined based on a previous study with a similar design (99). The power was set to 80%, alpha to 5%, and the correlation coefficient for the null hypothesis (no correlation) to 0.30 (100).

Ordinal data were reported as the medians and interquartile ranges, and continuous variables were presented as the means and SDs. Internal consistency and reliability between the different SF-36 items were calculated using Cronbach's alpha. For all statistical tests, alpha was set at 0.05, and all tests were 2-tailed. Within-subject Spearman correlation coefficients and their corresponding p-values (95% CIs) were calculated. We compared the data in our study with data from a healthy population from a study examining the use of the SF-36 (89) in the general population in the same geographical area in Sweden. We used the mean, SD and population size in each study and ran t-tests on the values. The correlations between the one-dimensional scales and all domains of the SF-36 were measured using Spearman's rho for categorical variables and Pearson's r for continuous variables. In study III and IV, Quality Metric Health Outcomes™ Scoring Software 4.0 was used to calculate the summary scores for the different SF-36 domains. Internal consistency and reliability between the different SF-36 items were calculated using Cronbach's alpha for comparing groups, and α values greater than 0.70 were regarded as representing acceptable reliability (101).

4.8 Ethical consideration

All studies were approved by the Regional Ethical Review Board in Gothenburg, Sweden (study I; registration number 157/11), (study II; within the framework of the Skaraborg Project), (study III and IV; registration number 786-11). Written and oral information about the studies was given to the participants, and informed written consent was obtained from all participants prior to their participation. The participants were allowed to withdraw from the studies at any point without giving a reason.

5 RESULTS

5.1 The perception of dyspnea in every-day life – (I)

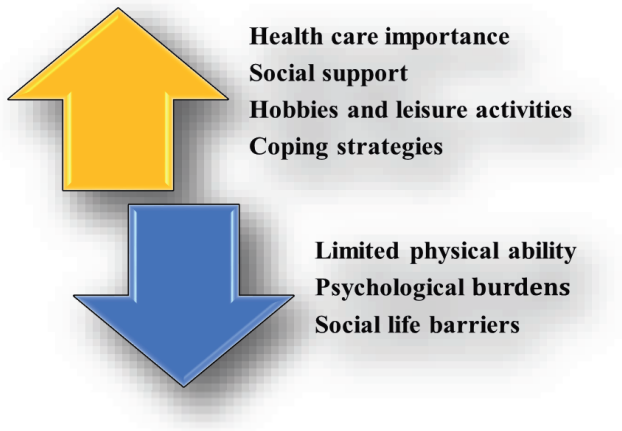
In the first study, 20 patients were included. Sixteen of them (nine men, seven women) successfully used their diaries for the seven planned consecutive days. Five of the participants had diagnoses of COPD (four women, one man), six had diagnoses of heart failure (one woman, five men), three had an anxiety disorder (all female), one had aortic stenosis (male) and one had a diagnosis of asthma (female). Seven participants had a history of smoking (five smokers and two former smokers).

The content analysis of the diaries showed 21 subcategories and eight categories, and after further analysis in our discussions, we found two main themes: (I) Impaired QoL and (II) Symptom tolerance and adaptation. Patients had an impaired QoL due to their limited capacity for physical activity, which was the most common consequence of dyspnea in participants' everyday lives. The other reasons for patients' reduced QoL were obstacles in their social lives and the fact that they were psychologically burdened by dyspnea.

5.2 The multidimensionality of dyspnea

They described the burden of dyspnea in many terms and in many situations, which gave a clear picture of the multidimensionality of dyspnea. Tiredness and a lack of energy, negative influences on social relationships, its impact on their general well-being, unhappiness, fatigue, run-down feelings or insomnia, stress, anger, fear, and anxiety were some of the terms they used in describing how they felt when experiencing symptoms of breathlessness. The participants indicated that they were able to tolerate the severity of their symptoms with appropriate medication and/or if they had support from their family or if they were involved in some activities, and they had developed different coping strategies. The following categories were finally considered: the importance of health care, social support, hobbies and leisure activities and coping strategies. These categories represent the ways in which patients sought solutions to problems they experienced due to breathlessness.

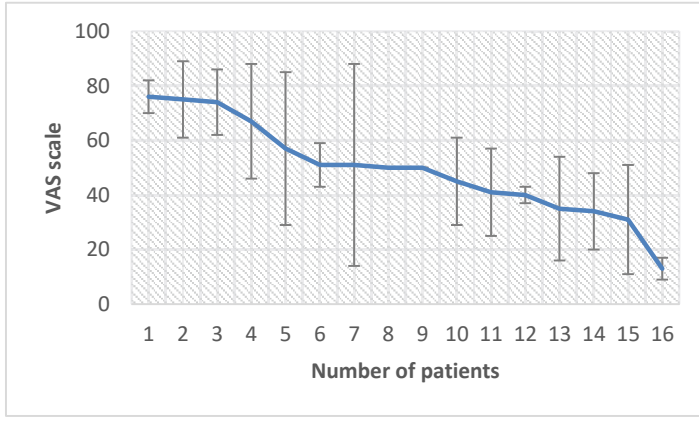
Figure 3. Categories describing how patients suffering from breathlessness experience their everyday life



5.3 The variability of perceived dyspnea

The severity of dyspnea showed significant variability, as displayed by the VAS results (I). Minimum, maximum, and mean values were calculated and are shown in *Figure 4*.

Figure 4. Daily VAS-scores for participants (n=16): mean, minimum and maximum values



5.4 "Sensing" the symptom before the outbreak of the disease – (II)

Participants (n=1,038) with a mean age of 51 years and equally distributed between men and women were examined via echocardiography and had their Nt-proBNP concentrations analyzed; 901 participants had regular left ventricular diastolic function, and 137 suffered from diastolic dysfunction. Significantly more males (n=79) than females (n=58) ($p < 0.001$) were diagnosed with DD-PSF, and in both sexes, those with DD-PSF were considerably older than in those with regular diastolic function. In total, 39 individuals, 23% of the total participants with DD-PSF, reported their SRH as poor or very poor. In the multivariate binary regression analysis, the following covariates were mutually entered into the same model: age, sex, SRH, Nt-proBNP, diabetes mellitus, obesity, hypertension, left ventricular hypertrophy, and heart rate. We found both low SRH (OR 2.95; 95% CI 1.02–8.57) and Nt-proBNP concentrations (quartile 4 vs. quartile 1 OR 4.23; 95% CI 1.74–10.26) to be significantly associated with DD-PSF (Table 2). The results showed an association between SRH and cardiovascular diseases that was similar to previous findings (102) and demonstrated the importance of this "self-sensing" of having a disease. Patients with breathlessness showed similar sensing in terms of poorer SRH even in those with heart failure. The analysis showed that breathlessness or shortness of breath was among the three symptoms which remained associated (OR 1.5; 95% confidence interval 1.1-2.0) with SRH when multiple symptoms were examined in a regression analysis (103). This information is clinically useful and adds another clue that may facilitate a targeted approach to the assessment of dyspnea

Table 2. Multivariate logistic regression analysis of factors associated with LVDD-PSF

Covariates	Odds ratio	95% CI	p-value
Age	1.12	1.09–1.15	0.001
Covariates* in model:			
Sex (female)	1.64	0.87–2.72	0.056
SRH (poor- very poor)	2.95	1.02–8.57	0.047
Nt-proBNP (pg/ml)**			
Quartile 1 ≤ 203	1	-	-
Quartile 2 204-406	2.82	1.13–7.05	0.026
Quartile 3 407-727	3.59	1.46–8.84	0.006
Quartile 4 ≥ 728	4.23	1.74–10.26	0.001
DM T2	1.44	0.70–2.97	0.322
Obesity	1.17	0.65–2.09	0.586
Hypertension	1.77	1.03–3.05	0.040
Heart rate	1.04	1.01–1.07	0.005
LVH	5.76	3.28–10.13	0.001

Note: Associations were estimated using a binary logistic multivariate regression and expressed as ORs (odds ratios) with 95% CIs (95% confidence intervals).

* Covariates in the model were; Sex, SRH (self-rated health), Nt-ProBNP (N-terminal pro-brain natriuretic peptide), DM T2 (diabetes mellitus type 2), Obesity, Hypertension, Heart rate, and LVH (left ventricular hypertrophy).

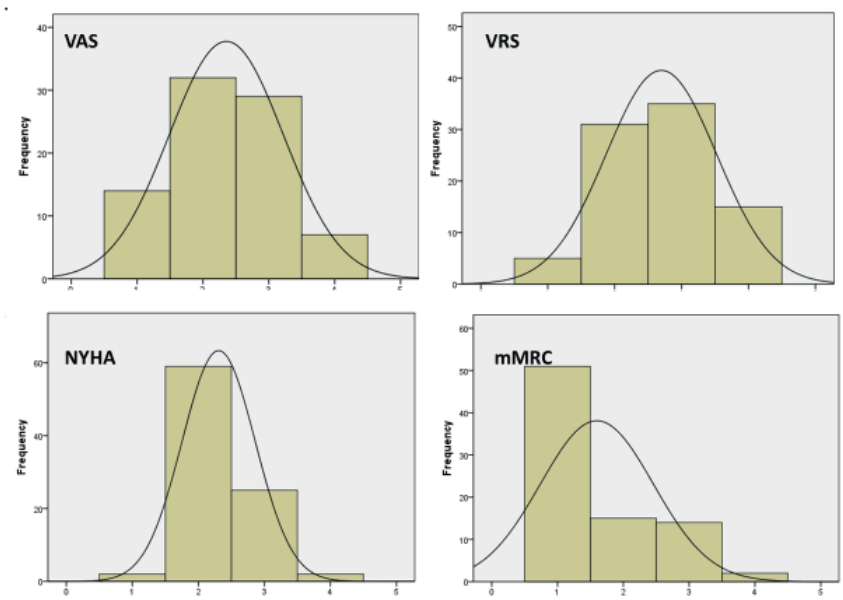
LVDD-PSF (Left ventricular diastolic dysfunction with preserved systolic function)
** Values for Nt-proBNP are expressed as quartiles (q1-q4)

5.5 HRQoL impacted by the intensity and severity of dyspnea – (III)

5.5.1 Measurement of dyspnea

The reported values from the NYHA scale, VRS, and VAS displayed a normal distribution. By contrast, the distribution of mMRC scores was rather skewed,

Figure 5. The distribution patterns of the NYHA scale, mMRC scale, VRS, and VAS scores



as depicted in Figure 5, which confirmed the discriminative features of the mMRC scale. The frequencies, means, and medians, are provided in Table 3. These demonstrate that a dyspnea intensity level at a frequency of almost 70% corresponds to the NYHA class II category, and this value was equivalent to the frequencies on the mMRC scale for grades one and two combined. VRS and VAS were more equally and similarly distributed in grades two and three.

Table 3. Characteristics of interrelationships for each one-dimensional scale

Frequency (%)	NYHA I-IV grades	VRS 1-4 grades	mMRC 0-4 grades	VAS 0-4 grades
0	-	-	-	-
1	3 (3.4)	5 (5.6)	51 (57.3)	14 (15.7)
2	61 (68.5)	33 (37.1)	18 (20.2)	32 (36.0)
3	22 (24.7)	33 (37.1)	11 (12.4)	29 (32.6)
4	2 (2.2)	15 (16.5)	2 (2.2)	7 (7.9)
Missing	1 (1.1)	3 (3.4)	7 (7.9)	7 (7.9)
Mean (SD)	2.26 (0.56)	2.67 (0.83)	1.56 (0.84)	2.36 (0.86)
Median	2	3	1	2

New York Heart Association (NYHA), Modified Medical Research Council (mMRC) scale, Verbal Rating Scale (VRS), Visual Analogue Scale (VAS). The mean, standard deviation (SD), and median are presented

5.5.2 Correlation of instruments

Table 4 shows the correlation coefficients between the intensity and severity of dyspnea rated by all four one-dimensional scales, as well as that between results of the one-dimensional scales and the eight individual domains of the SF-36, with the results from male and female participants in separate columns. The correlation between the results of the one-dimensional scales (i.e., the VAS and all domains of the SF-36) is shown for categorical variables (Spearman's rho) and continuous variables (Pearson's r).

The correlation between scores from the NYHA and mMRC scales was ($r = 0.67$, $p<0.010$). The correlation between scores from the NYHA scale and the VRS was non-significant and weak compared with the correlation between scores from the NYHA scale and the VAS among females. The NYHA scale scores were significantly correlated with results for some of the SF-36 domains, such as Physical Functioning, Role Functioning, General Health, and Vitality. Results for Social functioning differed between men and women. The mMRC scale scores showed a highly significant correlation with both the VRS and VAS scores. The mMRC scale scores were correlated with the results for the domains Physical Functioning, Role Functioning, General Health, and Vitality in the SF-36. VAS scores were positively associated with VRS scores ($r=0.50$, $p<0.010$), and the scores of both were correlated with the results for the domains Physical Functioning and Role Functioning, whereas the NYHA and mMRC scale scores were correlated with a significantly greater number of

domains. However, the latter demonstrated the best ability to reflect HRQoL because of its greater correlation with different domains of the SF-36, shown in bold in *Table 4*.

Table 4. The correlation between the four one-dimensional scales and different domains of the SF-36

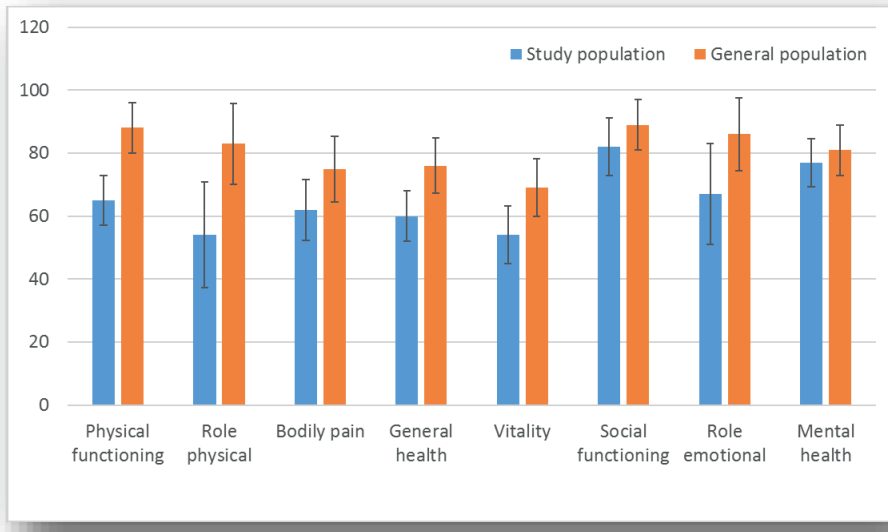
		NYHA			mMRC			VRS			VAS		
		All	♀	♂	All	♀	♂	All	♀	♂	All	♀	♂
Dyspnea scales	NYHA	-											
	mMRC	**0.67**	**0.62**	**0.76**	-								
	VRS	*0.32*	0.24	**0.37**	**0.39**	**0.43**	**0.37**	-					
	VAS	0.28	0.04	**0.55**	*0.32*	0.10	**0.55**	**0.50**	**0.34**	**0.65**	-		
Domains of the SF-36	PF	**-0.40**	**-0.47**	**-0.35**	**-0.51**	**-0.55**	**-0.48**	**-0.45**	**-0.48**	**-0.42**	*-0.33*	-0.25	**-0.42**
	RP	*-0.34*	*-0.31*	*-0.34*	**-0.41**	**-0.54**	**-0.33**	*-0.41*	*-0.40*	*-0.43*	**-0.48**	**-0.43**	**-0.51**
	BP	-0.21	-0.26	-0.17	-0.21	**-0.35**	-0.12	-0.25	**-0.51**	-0.02	-0.17	-0.33	-0.04
	GH	-0.29	-0.29	-0.28	**-0.32**	-0.24	**-0.40**	-0.27	-0.17	**-0.38**	-0.26	-0.20	*-0.33*
	VT	*-0.33*	-0.23	**-0.41**	**-0.39**	*-0.32*	**-0.48**	-0.25	-0.17	-0.28	-0.26	-0.14	*-0.35*
	SF	-0.29	-0.19	**-0.37**	-0.27	-0.14	**-0.40**	-0.12	-0.10	-0.15	-0.23	-0.03	*-0.37*
	RE	-0.27	-0.18	*-0.34*	-0.25	-0.17	*-0.33*	-0.25	-0.18	*-0.32*	-0.20	-0.08	-0.27
	MH	-0.19	-0.21	-0.12	-0.23	-0.23	-0.24	-0.08	-0.04	-0.18	-0.04	-0.26	-0.21

New York Heart Association (NYHA), modified Medical Research Council (mMRC) scale, Verbal Rating Scale (VRS), Visual Analogue Scale (VAS), SF-36 domains: Physical Functioning (RF), Role-Physical (RP), Bodily Pain (BP), General Health (GH), Vitality (VT), Social Functioning (SF), Role-Emotional (RE), Mental Health (MH)
Bold Correlation is significant at the 0.01 level (2-tailed); *Italics* Correlation is significant at the 0.05 level (2-tailed)

5.5.3 Dyspnea and the health-related quality of life

Compared with previously published mean SF-36 scores for the general population (89), the scores of patients in our study (III) were significantly lower for seven of the eight domains of the SF-36, most prominently for Physical Functioning, General Health, Body Pain, Vitality, and Role Functioning ($p<0.001$). The mean SF-36 scores in each domain are shown in Figure 6. Items included in all domains showed satisfactory internal consistency, which confirms the satisfactory homogeneity and reliability of the mean scores obtained from the SF-36.

Figure 6. Scores of the eight domains included in the SF-36 in our study compared with those in the general population



The data obtained from different domains of the SF-36 were compared with data from a study by Sullivan et al. "Social Science & Medicine. 1995;41(10):1349-58" conducted in the general population in Western Sweden.

5.6 Prevalence and treatment – (IV)

The prevalence ratio was calculated by dividing the number of patients identified with dyspnea (n=115) in study III by the number of all actively listed patients in Orust (n=8800), giving a value of 1.3 percent for the inclusion time (study III).

After categorization into three groups (patients with no suspected cardiovascular or pulmonary disease were excluded after initial assessments) we identified 40 patients (15 women) with a cardiovascular disease, 21 patients with a pulmonary disease (12 women), and 17 patients with psychiatric disorders (nine women). Patients with a cardiovascular disease were significantly older than the other groups (age 71.5 (SD 9.5) years, $p < 0.02$). Nt-proBNP, a marker for heart failure, was present in significantly higher concentrations in patients with a cardiovascular disease in comparison with all

participants ($p < 0.001$). However, there were no significant differences in smoking habits or comorbidities, such as hypertension or diabetes mellitus type 2, among the groups.

Beta-blockers were the most frequently used drug, being used by 52% of patients with a cardiovascular disease and 44% of patients with a pulmonary disease, and angiotensin-converting enzyme inhibitors were the second most commonly used drug, being used by 17 and 33% of patients, respectively. Angiotensin II receptor blockers were used more frequently (37%) by patients with cardiovascular diseases than by patients with pulmonary diseases (5%). All patients with pulmonary diseases received bronchodilators alone or in combination with steroids. Details are displayed in Table 5.

Table 5. Baseline characteristics of the study participants

Characteristics	All baseline n = 89	Cardio-vascular diseases n = 40	P value	Pulmonary diseases n = 21	P value	Psychiatric disorders n = 17	P value
	Mean (SD)	Mean (SD)		Mean (SD)		Mean (SD)	
Age – yrs	68 (10)	71 (9)	0.021	68 (8)	0.921	65 (12)	0.039
Systolic BP mmHg	139 (15)	141 (18)	0.270	137 (16)	0.610	136 (14)	0.355
Diastolic BP mmHg	78 (10)	78 (10)	0.869	75 (8)	0.295	77 (11)	0.795
BMI, kg m^{-2}	29 (5)	29 (5)	0.702	27 (6)	0.213	29 (5)	0.639
Nt-proBNP ng/L	572 (144)*	982 (281)*	0.005	379 (353)*	0.500	131 (28)*	0.115
	n (%)	**n (%)**	**P value**	**n (%)**	**P value**	**n (%)**	**P value**
Female sex	44 (49)	15 (37)	0.043	12 (67)	0.114	9 (47)	0.839
Hypertension	42 (47)	21 (57)	0.141	5 (28)	0.317	6 (37)	0.402
DM T2	7 (8)	5 (13)	0.264	1 (5)	0.586	1 (5)	0.637
Medication							
Beta-blocker	36 (40)	21 (52)	0.056	8 (44)	0.857	5 (29)	0.131
ACEI	16 (18)	7 (17)	0.615	6 (33)	0.159	3 (18)	0.763
ARB	26 (29)	15 (37)	0.174	1 (5)	0.095	6 (35)	0.813
Diuretic	25 (28)	13 (32)	0.931	7 (39)	0.478	5 (31)	0.939
Statins	26 (29)	15 (37)	0.130	8 (44)	0.124	2 (12)	0.036
ASA	26 (29)	14 (35)	0.340	7 (39)	0.113	3 (17)	0.141
SSRIs	9 (10)	2 (5)	0.077	1 (5)	0.909	8 (40)	0.005

Blood Pressure (BP), Body Mass Index (BMI), N-terminal B-Type Natriuretic Pro-peptide (Nt-proBNP), Angiotensin-Converting Enzyme Inhibitor (ACEI), Angiotensin II Receptor Blocker (ARB), Acetylsalicylic Acid (ASA), Selective Serotonin Reuptake Inhibitors (SSRIs), Mean (Standard Error)
#Seven participants were undiagnosed, three participants had combined CHG-COPD, and one death occurred (all excluded)
*mean and (standard error)

5.7 Underlying aetiologies and comorbidities – (IV)

In patients with cardiovascular disease (n=40), we found eighteen cases of hypertension (20%), nine cases of heart failure (10%), four cases of atrial fibrillation, six cases of valvular diseases, and three cases of IHD. In the group with pulmonary diseases, we found thirteen cases of COPD, five cases of restrictive lung diseases and three cases of asthma. Details are shown in Table 6.

Table 6. The frequency and proportion of comorbidities in the study population

	Frequency	**Percent**
Cardiovascular diseases	*(40)*	*(45%)*
Hypertension	18	20
Heart failure (HF)	9	10
Atrial fibrillation (A-Fib)	4	4.4
Mitral regurgitation (MR)	3	3.4
Ischaemic heart disease (IHD)	3	3.4
Aortic regurgitation (AR)	2	2.2
Aortic stenosis (AS)	1	1.1
Pulmonary diseases	*(21)*	*(24%)*
Chronic obstructive pulmonary disease (COPD)	13	14.5
Restrictive lung disease (2) + Obesity (3)	5	5.6
Asthma	3	3.3

5.8 Changes in dyspnea over time – (IV)

After one year, we found that the one-dimensional scale (mMRC, VAS and VRS) results did not show a worsening of dyspnea. By contrast, VAS scale results showed a significant improvement in the severity of dyspnea in the cardiac disease group. A corresponding improvement was not observed in patients with pulmonary disease-associated dyspnea. The results for the eight different domains of the SF-36 did not show any significant changes in either disease category.

6 DISCUSSION

6.1 General discussion of the results

6.1.1 Main findings

In our first study, we used a qualitative design with content analysis and used diaries as data-collecting tools. Diaries gave us extraordinary insight into patients' everyday lives. Using diaries made a significant contribution to our understanding of how patients with perceived dyspnea cope with the severity of their symptoms in their every-day activities. We also found variability in the intensity of dyspnea both on the individual and collective level.

In study II we found an association between SRH, Nt-proBNP, and hypertension, respectively, with diastolic dysfunction. Identifying patients with diastolic dysfunction in primary health care is essential as a preventive measure for treating heart failure at a later stage. A decade ago, Palmieri et al. noted in their study that "Isolated LV diastolic dysfunction was independently associated with lower peak exercise LV systolic performance in patients without CHF. Its diagnosis may provide a target for aggressive CHF risk management (104)."

In study III we investigated different tools for measuring dyspnea in relation to various domains of the SF-36. Dyspnea primarily impacted physical activity as demonstrated by the correlation with the physical domains of the SF-36. Impaired HRQoL, compared with that of the general population, was confirmed in our study using the SF-36.

In study IV we followed up patients with both respiratory and cardiovascular diseases one year after the first contact. Monitoring long-term changes in dyspnea gave us information about which category of patients benefited from treatment and how they rated their level of improvement. We identified the underlying diseases and found the prevalence of dyspnea in the primary health care centre to be representative for small communities in Sweden.

6.1.2 The perception of dyspnea *in every-day life (I)*

Examining dyspnea from the patients' points of view gives us valuable insight about the impact of dyspnea in patients' day-to-day lives; furthermore, the fact that it is a subjective symptom makes it a suitable object of study in qualitative investigations (105). How patients rate their health status via their own descriptions can be helpful in planning more individualized care in the long

run. It can also improve the satisfaction of caretakers and allow caregivers to pay more attention to the needs and expectations of individual patients. Patients' and physicians' perceptions of the actual situation are not always the same. To understand this, we wanted to look at this matter closer.

The description of breathlessness in heart failure patients (106) and patients with cancer or COPD (107) shows similar patterns, which leads to a fundamental question regarding the similarities in the neurobiological circuitry of dyspnea and whether dyspnea should be treated as a stand-alone symptom regardless of origin, similar to how pain is treated. This matter should be studied in larger clinical randomized studies. Baily et al. highlighted in their paper the importance of the non-pharmacological management of breathlessness (108), and in our study, we saw how participants reported their different strategies for coping with breathlessness in daily life.

6.1.3 "Sensing" the symptom before the outbreak of the disease (II)

The findings of this study need to be replicated in other populations and especially utilizing a cohort design if SRH is to be considered as a new complementary tool in the investigational toolbox of healthcare workers for assessing the early stages of heart failure. Furthermore, the strong correlation found here between poor SRH and DD-PSF, which remained even after adjustments for age and sex, gives rise to another important question, namely, whether left ventricular dysfunction is as "asymptomatic" as previously claimed. By contrast, the results of the present study clearly indicate that patients with DD-PSF have an awareness of their illness.

The association between SRH and the incidence of cardiovascular disease has been discussed in previous studies (102). Benyamini et al. (109) showed that physical sensations may be manifestations of illness and can act as powerful indicators of potentially future health risks. The majority of participants in our study rated their health status as good or very good despite the prevalence of co-morbidities among them. The Cardiovascular Health Study (CHS), with eight years of follow-up of patients with a mean age of 73 years, showed that SRH declined two years before death compared with SRH in the "no event" group. Additionally, a worsening of SRH among 625 participants predicted the onset of heart failure.

Cardiac markers, such as natriuretic peptides, have also been used in identifying heart failure separate from the use of health metric methods such as SRH (II). Elevated Nt-proBNP concentrations in patients with DD-PSF have been shown (110,111), and SRH has also been shown to be associated with biomarker levels (112). In a systematic review, the authors showed that the

absolute risks of progression to heart failure were three times greater for those with asymptomatic diastolic dysfunction than for those without any ventricular dysfunction (113). This raises the question of whether Nt-proBNP, as a marker of heart failure, is useful in the early selection of these patients and if there is any association with how these patients rate their health using a single question (SRH). These findings should also help us address the interesting question of whether asymptomatic diastolic dysfunction is actually asymptomatic. In another study, breathlessness or shortness of breath was shown to be associated with poorer SRH (103). Since breathlessness is a major symptom of heart failure, these findings suggest the importance of examining SRH together with other predictors of heart failure. A cohort study including 5,301 individuals with suspected heart failure identified 439 (17%) individuals with asymptomatic diastolic dysfunction by the time of the out-patient appointment (NYHA class I). In these patients, asymptomatic left ventricular systolic dysfunction was associated with reduced peak exercise capacity, renal impairment, cardiac conduction tissue disease and a significantly elevated risk of mortality. Therefore, classifying them as having 'mild' heart failure as suggested by the NYHA classification was not recommended. The authors concluded that a lack of symptoms leads to complacency about initiating optimal therapy (114).

Therefore, our results show the significance of considering SRH in association with a biomarker for heart failure (e.g., Nt-proBNP), which has also been mentioned by Farkas et al. (115), despite the limited size of their study sample. Our study thus adds additional knowledge concerning the utility of SRH for research purposes, but its practical benefits must be studied further in association with DD-PSF (II).

6.1.4 HRQoL impacted by dyspnea (III & IV)

The study results demonstrate that patients presenting with dyspnea experience an overall reduction in their HRQoL compared with that of the general population (116). The most affected domains examined by the SF-36 were physical function, general health, vitality, body pain, and social functioning. The multi-item SF-36 questionnaire provides significant information about the multi-dimensionality of dyspnea (63) and the burden it presents to affected patients in the primary health care setting.

6.2 Measurement of dyspnea

6.2.1 The intensity and severity of dyspnea (III)

The ATS highlights three previously mentioned domains related to measurements of dyspnea: sensory perception, affective distress, and the burden of the symptom, and all three domains were chosen based on investigating more than 50 different measures of dyspnea (7) without finding any dyspnea-related measures outside the framework constructed by these three domains.

Therefore, caregivers can choose an appropriate measure of dyspnea based on the actual situation, the underlying disease and the type of domain examined. The question is which instrument fits best and is most suitable for use in primary health care settings. We hypothesized that the instrument that covers the most domains of the SF-36 would be the most appropriate measurement tool. The categorizations of one-dimensional and multidimensional measurement scales are based on Dorman's review of scales for measuring dyspnea in palliative care. The dimension measured could be the intensity or the sensory quality of dyspnea [Borg dyspnea scale, VAS, Numeric Rating Scale (NRS)] or the impact dyspnea has on functionality (mMRC, BDI/TDI) (117). Dorman and colleagues did a Cochrane-based review, and they identified 29 scales: six to measure breathlessness severity, four to assess breathlessness descriptions, and 19 to measure functional impacts of breathlessness. The NRS and the VAS were among the scales assessed, but both require larger sample sizes and evidence for the effectiveness of interventions. They concluded that there was a need for further evaluation before adopting any scale as a standard (117).

Bausewein et al. identified thirty-three tools for measuring dyspnea which were validated for use with advanced diseases such as cardio-respiratory disorders. Twenty-nine were multidimensional, 11 were breathlessness-specific and 18 disease-specific. Four tools were one-dimensional, measuring the severity of breathlessness. They did not find any tool that was able to measure all the dimensions of dyspnea (118).

In our study, we chose the VAS and VRS for measuring the intensity or severity of symptoms, and the NYHA and mMRC scales were selected for rating the impact of dyspnea on the physical ability of the patients. The SF-36 is widely used for investigating HRQoL, and it was suitable for use based on the design of our study. It was not surprising that the NYHA and mMRC scale results were closely correlated. The NYHA and mMRC scales cover many domains of the SF-36, confirming the utility of these scales in research and

especially in clinical settings. The mMRC scale has been suggested to be an adequate measurement tool for the diagnostic assessment of COPD (85,119). Our results confirmed that the mMRC questionnaire is a powerful measurement instrument (12,120) and show it to be a useful method for assessing dyspnea in a primary health care setting (118,121). We confirmed (IV) that the VAS, as a continuous scale, is more appropriate for monitoring long-term changes (122), and it was shown to be suitable for monitoring other subjective symptoms, such as pain and fatigue (123, 124).

6.2.2 Changes in dyspnea over time (IV)

In our study, patient-reported outcomes rated via one-dimensional scales and the SF-36 (a multi-dimensional scale) were measured among patients with perceived dyspnea in two different disease categories (cardiovascular and pulmonary diseases). Regarding our first research question, we found that the one-dimensional scales (mMRC, VAS, and VRS) did not show a worsening of dyspnea after one year of follow-up. By contrast, the VAS scale showed a significant improvement in the severity of dyspnea in the cardiac disease group, which could lead to better standardization of dyspnea outcome measures for more precise comparisons in the future (125). This result is consistent with those of previous studies (65,126). A corresponding improvement was not observed in patients with pulmonary disease-related dyspnea (127). There is no universal single management strategy for dyspnea. Different types of therapies, from yoga-based rehabilitation (128) to opioids (129), have been suggested. In any case, it is important to select a focused therapy to treat the identified underlying condition. Since treatment follow-up also demands a structure to rate the dyspnea, it is important to find a useful, valid and reliable instrument for the long-term follow-up of the patients with perceived dyspnea.

6.3 Methodological considerations

6.3.1 Design and sample size (I, III, IV)

We used different research designs for the studies in this thesis. The different designs gave us the opportunity to study dyspnea from different points of view depending on the research question and duration of the study. While the tradition in medical research has been mainly data oriented, qualitative research has also been performed based on narratives, interviews, and texts. Due to the inherent subjectivity of dyspnea, qualitative research with a focus on the experience of the individuals with perceived dyspnea was appropriate.

The implications of the results from each type of research differ and are dependent on the limitations and strengths of the particular study.

In our first study, we used a qualitative design with inductive content analysis. The advantages of the method were that it was easy for participants to understand and it required some reflection about the symptom, which was found to be a positive experience for patients. They described it as an opportunity to be aware of the intrinsic ability they had to handle their everyday activities in living with their breathlessness. The method was even more powerful when we used it as an inductive way to generate hypotheses when planning the other studies (III and IV). Replicating the study is straightforward, and therefore, it is easy to establish reliability.

Our second study was a population-based study using data from the Vara-Skövde Cohort. The strength of the study was the large population size and the quality of data used for determining risk factor-disease associations. We were able to calculate the prevalence of DD-PSF, which was a significant advantage of the study, and the logistic regression model was an appropriate method for examining multiple risk factors. The limitation of the study was the difficulty in establishing causality due to the cross-sectional design, and we lacked the follow-up data at that moment. We considered confounding variable that may interfere in estimating the associations between SRH, Nt-proBNP and DD-PSF, and we minimized their effects by using a multivariate logistic regression analysis.

Study III also had a cross-sectional design, but in this study, the small size of the study population was a limitation. The reason for the low number of recruited participants was the low number of consultations solely because of dyspnea in primary health care. An additional limitation was that we performed the study in only one health cantre. Compared with other studies asking the same questions, we thought the sample size for our studies were large enough for performing a multiple correlation analysis. Despite the the small sample size in study III and IV, we believe that the health centre from which data were collected is representative of the primary health care in the rural areas of Sweden. Although the study population was from a particular rural area, the results of the study could be representative of most communities of the same size in Sweden.

6.3.2 Health metric instruments

In the first study, we used diaries for the purpose of data collection (130,131). When we realized that patients had significantly reduced QoL, we thought that the SF-36 would be suitable, with all of its different subscales, for covering

many of the relevant QoL domains (132). Measurements of dyspnea can be conducted using a variety of different scales. In our study, we used a Likert scale (VRS) based on four different levels of symptom severity. However, measuring pain using a VRS has not been shown to give equivalent results relative to a VAS scale (83). A VAS has also been demonstrated to be superior in the characteristics of its metrics when compared with ordinal scales (82). Both a VAS and VRS are symptom-specific measurement scales. Thus, the next step in choosing appropriate measurement scales was to find a symptom-specific instrument, and since we expected that many of our study participants would have heart or lung diseases, the mMRC dyspnea scale and the NYHA scale were obvious choices. Both scales are widely used and have been validated in numerous studies (56,84,133). However, a recent study has shown that classifications of COPD using the mMRC or COPD assessment test (CAT) scores are not identical (134), which means that they cannot be interchangeably used for the classification of COPD, which is worth considering in clinical practice. In our study, we noticed that "the NYHA classification system is a valid measure of *functional status*, but strictly limited by many personal, social and environmental factors including symptoms. Thus, the NYHA classes should not be reported as measuring the QoL, physical ability, functional performance, or other concepts (133)".

6.3.3 HRQoL and SF-36

We compared the HRQoL in patients with dyspnea with the results a study reporting QoL in the general population in 1995 (89). Comparing the HRQoL in a representative population from 2013 with that from a population from 1995 can be questioned. A study conducted in 2003 was designed as a longitudinal study in a Swedish general population (N = 1 849) as a follow-up of the 1995 study assessing HRQoL using the SF-36. They reported that the most consistent finding was a better health outcome in the eight-year follow-up (135). However, we have no reason to assume that HRQoL among the Swedish general population has declined now compared to that in 2003 or 1995. As mentioned, the puzzle of dyspnea is complicated, and if we managed to uncover a small piece of the puzzle, we have taken a small step forward.

7 CONCLUSION

We analyzed dyspnea in four studies and performed both qualitative and quantitative analyses with different perspectives in mind. The existing approaches to the assessment of dyspnea in primary health care have the potential to be improved with the contribution of new results in the field of dyspnea research from recent decades. The results in the studies presented here emphasize a further understanding of dyspnea and highlight the importance of this multifaceted symptom. Measurements of dyspnea using multidimensional questionnaires are becoming more frequent in clinical medicine, but there is still no single measurement method that can be used in clinical settings. A measurement instrument must be easy for patients to understand and easy for caregivers to use. It should reflect the progression of the disease and have a good correlation with other relevant clinical parameters, such as FEV_1 or LVEF. It should allow for the severity of dyspnea to be rated and be an evaluative measure used to identify changes over time. One goal of this thesis was to evaluate the four most frequently used measurement instruments in order to find the most appropriate one to estimate both the severity of dyspnea and provide a good association with the patient´s QoL. Such instruments have an advantage in the follow up of patients in a primary health care setting and in the evaluation of the therapy provided. We also examined dyspnea both as a stand-alone symptom and as a component of chronic diseases. Based on the results of study IV, we suggest that both the mMRC scale and the VAS should be used in the assessment of dyspnea, depending on the purpose of the measurement. The VAS is particularly appropriate for use in long-term follow-ups, but the mMRC scale has highly effective features for evaluating dyspnea at a particular time.

Based on the results of previous studies, we knew that SRH was a strong indicator of cardiovascular incidents, and the association with diastolic dysfunction added yet another dimension to this easy to use yet powerful clinical instrument. SRH data can facilitate a targeted approach in the assessment of dyspnea. In our study, SRH was shown to be a reliable factor associated with diastolic dysfunction even after adjusting for possible confounding factors.

8 IMPLICATIONS

One approach to solving a problem involves having the opportunity to ask the right questions to reach the correct answer (136). Qualitative research is an appropriate technique when the goal is to generate hypotheses. Symptom research is not all about biomedical factors, and a biopsychosocial model must also be kept in mind. Qualitative research makes it possible to interpret personal experiences to explain health-related phenomena (137), which was the field we wanted to explore.

Results in the study II provide not only a new contribution to the body of knowledge concerning SRH in that regard to association with diastolic dysfunction, but also confirms that known risk factors, such as hypertension and obesity, are associated with DD-PSF. However, these findings need to be replicated in other settings and especially in studies utilizing a cohort design with an even larger sample size to determine if SRH should be considered as a new complementary tool in the investigational toolbox healthcare workers for assessing the early stages of heart failure. Furthermore, the strong association found here between poor SRH and DD-PSF, which remained even after adjustments for age and sex, gives rise to another important question: whether left ventricular dysfunction is as "asymptomatic" as previously claimed. By contrast, the results of the present study clearly indicate that patients with DD-PSF have an awareness of their illness, which should also be examined in more detail in future research.

In summary, the HRQoL of patients presenting with dyspnea is lower than that in the general population. The impact of dyspnea on patients' daily lives was reflected in the results of one-dimensional scales, such as the mMRC and NYHA scales, and was also in agreement with the results from similar one-dimensional scales as shown by the positive correlations. However, the mMRC scale was the most responsive scale in the current study and, therefore, may be a superior rating instrument for assessing dyspnea in primary health care settings. The mMRC scale results also showed correlations with several dimensions of the SF-36, which is clinically relevant. These findings offer an excellent opportunity to understand more about dyspnea and can be used clinically in the early assessment of this disorder (III). In his study, Voll-Aanerud concluded "In a general population sample, the burden of respiratory symptoms is more strongly associated with generic HRQoL than is lung function" (138).

Despite the few observational studies describing longitudinal changes in dyspneic patients, more knowledge is needed in this important area. We found minimal improvements in the general health and vitality of patients with

cardiac and pulmonary diseases after one year of conventional treatment. In a recent study, an affective/emotional dimension was linked to dyspnea (139), but the mental health domain showed no changes over time in our study. We suggest that one-dimensional scales, such as the mMRC scale and particularly a VAS, are appropriate measurements for the long-term assessment of dyspnea.

As mentioned before, the puzzle of dyspnea is complicated, and if we managed to uncover a small piece of the puzzle, we have taken a small but significant step forward. However, more research is needed to understand the enigmatic nature of dyspnea in order to solve the puzzle in due course.

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12 APPENDICES

12.1 Appendix 1, One-dimensional scales

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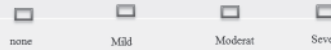
Appendix 1. The four one-dimensional scales used in the studies

Visual Analogue Scale
(VAS)

Verbal Rating Scale
(VRS)



New York Heart Association functional classification scale
(NYHA)

klass	Symtom
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in dyspnea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

Modified Medical Research Council dyspnea scale
(mMRC)

Grad	Symtom
0	I only get breathless with strenuous exercise
1	I get short of breath when hurrying on level ground or walking up a slight hill
2	On level ground, I walk slower than people of the same age because of breathlessness, or I have to stop for breath when walking at my own pace on the level
3	I stop for breath after walking about 100 yards or after a few minutes on level ground
4	I am too breathless to leave the house or I am

NB: This is the modified MRC scale that uses the same descriptors as the original MRC scale in which the descriptors are numbered 1-5. The modified MRC scale (0-4) is used for calculation of BODE index.

Dennis E. Doherty, MD, FCCP, Mark H. Belfer, DO, FAAFP, Stephen A. Brunton, MD Leonard Fromer, MD, Charlene M. Morris, MPAS, PA-C, Thomas C. Snader, PharmD, CGP, FASCP. Chronic Obstructive Pulmonary Disease: Consensus Recommendations for Early Diagnosis and Treatment. Journal of Family Practice, November, 2006.

12.2 Appendix 2, SF-36

36-Item Short Form Survey Instrument (SF-36)

RAND 36-Item Health Survey 1.0 Questionnaire Items

Choose one option for each questionnaire item.

1. In general, would you say your health is:

- 1 - Excellent
- 2 - Very good
- 3 - Good
- 4 - Fair
- 5 - Poor

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2. **Compared to one year ago**, how would you rate your health in general **now**?

- 1 - Much better now than one year ago
- 2 - Somewhat better now than one year ago
- 3 - About the same
- 4 - Somewhat worse now than one year ago
- 5 - Much worse now than one year ago

The following items are about activities you might do during a typical day. Does **your health now limit you** in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
3. **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	○ 1	○ 2	○ 3
4. **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	○ 1	○ 2	○ 3
5. Lifting or carrying groceries	○ 1	○ 2	○ 3
6. Climbing **several** flights of stairs	○ 1	○ 2	○ 3
7. Climbing **one** flight of stairs	○ 1	○ 2	○ 3
8. Bending, kneeling, or stooping	○ 1	○ 2	○ 3
9. Walking **more than a mile**	○ 1	○ 2	○ 3
10. Walking **several blocks**	○ 1	○ 2	○ 3
11. Walking **one block**	○ 1	○ 2	○ 3
12. Bathing or dressing yourself	○ 1	○ 2	○ 3

During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of your physical health**?

	Yes	No
13. Cut down the **amount of time** you spent on work or other activities	1	2
14. **Accomplished less** than you would like	1	2
15. Were limited in the **kind** of work or other activities	1	2
16. Had **difficulty** performing the work or other activities (for example, it took extra effort)	1	2

During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)?

	Yes	No
17. Cut down the **amount of time** you spent on work or other activities	1	2
18. **Accomplished less** than you would like	1	2
19. Didn't do work or other activities as **carefully** as usual	1	2

20. During the **past 4 weeks**, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

- 1 - Not at all
- 2 - Slightly
- 3 - Moderately
- 4 - Quite a bit
- 5 - Extremely

21. How much **bodily** pain have you had during the **past 4 weeks**?

- 1 - None
- 2 - Very mild
- 3 - Mild
- 4 - Moderate
- 5 - Severe
- 6 - Very severe

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22. During the **past 4 weeks**, how much did **pain** interfere with your normal work (including both work outside the home and housework)?

- 1 - Not at all
- 2 - A little bit
- 3 - Moderately
- 4 - Quite a bit
- 5 - Extremely

These questions are about how you feel and how things have been with you **during the past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the **past 4 weeks**...

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
23. Did you feel full of pep?	1	2	3	4	5	6
24. Have you been a very nervous person?	1	2	3	4	5	6
25. Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
26. Have you felt calm and peaceful?	1	2	3	4	5	6
27. Did you have a lot of energy?	1	2	3	4	5	6
28. Have you felt downhearted and blue?	1	2	3	4	5	6
29. Did you feel worn out?	1	2	3	4	5	6
30. Have you been a happy person?	1	2	3	4	5	6
31. Did you feel tired?	1	2	3	4	5	6

32. During the **past 4 weeks**, how much of the time has **your physical health or emotional problems** interfered with your social activities (like visiting with friends, relatives, etc.)?

- 1 - All of the time
- 2 - Most of the time
- 3 - Some of the time
- 4 - A little of the time
- 5 - None of the time

How TRUE or FALSE is **each** of the following statements for you.

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
33. I seem to get sick a little easier than other people	1	2	3	4	5
34. I am as healthy as anybody I know	1	2	3	4	5
35. I expect my health to get worse	1	2	3	4	5
36. My health is excellent	1	2	3	4	5