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Appetite in patients with heart failure

-Assessment, prevalence and related factors

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To my family
Henrik, Madeleine and Mathias

“The appetite grows for what it feeds on”

- *Ida B. Wells* -

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ABSTRACT

Background: Appetite is an important component in nutrition for maintaining the food intake needed by the body. Decreased appetite is a common clinical problem in patients with heart failure. It has a negative impact on food intake and possibly on malnutrition and health outcomes. There is a lack of evidence on how to assess appetite in heart failure. Furthermore, there are knowledge gaps about factors associated with appetite and which role appetite plays for health status in heart failure.

Aim: The overall aim of the thesis was to investigate appetite in patients with heart failure. Four studies were conducted with the goal to evaluate the psychometric properties of the Council on Nutrition Appetite Questionnaire (CNAQ) (I) and to explore the prevalence of decreased appetite and related factors associated with appetite in patients with heart failure (II-IV).

Methods: A multicenter study was conducted in three outpatient heart failure clinics in the center of Sweden during 2009-2012. Data were collected through a baseline measurement (I-IV) and an 18-month follow-up (IV). The first study was a psychometric evaluation study (I), while the other studies had an observational cross-sectional design (II-III) and an observational prospective design (IV). One hundred and eighty-six patients diagnosed with heart failure and experiencing heart failure symptoms participated at baseline. At the 18-month follow-up study (IV), one hundred and sixteen participants from the baseline participated. Data were collected from medical records (pharmacological treatment, comorbidity, left ventricle ejection fraction, time of diagnosis), self-reported questionnaires (demographic background data, appetite, symptoms of depression, health status, sleep, self-reported physical activity), objective

measurements (anthropometric assessment of body size, blood samples, six minutes' walk test, and physical activity measured with an actigraph) and clinical assessment (New York Heart Association (NYHA) functional classification, and cognitive assessment). The main outcome variables included appetite (I, II and IV) and health status (III). Descriptive and inferential statistics were used in the studies (I-IV).

Results: The majority of the participants had moderate heart failure symptoms, i.e., NYHA class II (n=114, 61%). Most of the participants were men (n=130, 70%). Mean age was 70,7 years, (SD=11,0), and mean BMI was 28.7 (SD=5.3). The CNAQ showed acceptable psychometric properties for assessing appetite in patients with heart failure (I). This thesis shows that 38% of the participants experienced an appetite level that put them at risk of weight loss (I). It was shown that factors such as biological, medical, psychological (II) and physical activity/exercise capacity (IV) are associated with appetite. Also, appetite was associated with impaired health status. However, this association was found to be moderated by symptoms of depression (III). Neither appetite nor physical activity changed during the 18-month follow-up (IV).

Conclusion: Decreased appetite is a serious phenomenon that needs attention in the care of patients with heart failure. Health care professionals can now use a validated and simple appetite instrument to assess appetite in heart failure. In addition, attention should be paid to elderly patients and those who have symptoms of depression, sleep problems, impaired cognitive function and impaired physical activity, as well as to patients on suboptimal medical treatment. Higher appetite was shown to contribute to a better health status, but this was only evident in patients without symptoms of depression. Therefore, special attention should be paid to symptoms of depression, as this risk factor affected the association between appetite and health status. This thesis enhances the understanding of the magnitude of the problem with decreased appetite in

heart failure both in numbers and factors. New priorities in nutrition care and new ideas can be established, both in practice and in research, in order to improve a nutrition care that is vital for patients with heart failure.

Keywords: Appetite, Age, Cognitive function, Depression, Health status, Heart failure, Malnutrition, Physical activity, Psychometrics, Pharmacotherapy, Sleep

LIST OF PAPERS

This thesis is based on the following papers, which will be referred to by their roman numerals.

- I. Christina Andreae, Anna Strömberg, Richard Sawatzky and Kristofer Årestedt. Psychometric evaluation of two appetite questionnaires in patients with heart failure. *Journal of Cardiac Failure* 2015;21(12):954-958.
- II. Christina Andreae, Anna Strömberg and Kristofer Årestedt. Prevalence and associated factors for decreased appetite among patients with stable heart failure. *Journal of Clinical Nursing* 2016;25(11-12):1703-1712.
- III. Christina Andreae, Anna Strömberg, Misook L Chung, Carina Hjelm and Kristofer Årestedt. Depressive symptoms moderate the association between appetite and health status in patients with heart failure. *Journal of Cardiovascular Nursing* 2018;33(2):E15-E20.doi: 10.1097/JCN.0000000000000428.
- IV. Christina Andreae, Kristofer Årestedt, Lorraine Evangelista and Anna Strömberg. The relationship between physical activity and appetite in patients with heart failure – a prospective and observational study. Submitted.

ABBREVIATIONS

CCI	Charlson Comorbidity Index
CNAQ	Council on Nutrition Appetite Questionnaire
ESS	Epworth Sleepiness Scale
EQ-5D	European Quality of Life-5 Dimensions
HF	Heart Failure
IHD	Ischemic Heart Disease
LVEF	Left Ventricle Ejection Fraction
MISS	Minimal Insomnia Symptom Scale
MMSE	Mini Mental State Examination
NYHA	New York Heart Association Classification
PHQ-9	Patient Health Questionnaire 9 item
SNAQ	Simplified Nutritional Appetite Questionnaire

INTRODUCTION

Nutrition is the food intake in relation to bodily needs and it is fundamental for all life processes including growth and health in particular. It is even more important in patients with chronic diseases who are affected by abnormal inflammatory and metabolic processes that can lead to malnutrition [1, 2]. This in turn creates great care needs due to medical complications, decline in functional capacity, impaired quality of life, longer length of hospital stay and poor survival rates [2-6]. Appetite is an important component for food intake and for maintaining weight [7]. Decreased appetite is a clinical problem in chronic illness, such as in patients with heart failure (HF). Heart failure is one of the most serious cardiac conditions worldwide and is associated with high morbidity and mortality rates. Although research has led to great improvements in the treatment and care of patients with HF [8-10], it remains a life-threatening syndrome that cannot be cured. The goal of the treatment is to relieve HF symptoms and improve prognosis [9, 11].

To date, most of the evidence for the management of decreased appetite has focused on identified pathophysiological factors for decreased appetite [12-15]. However, this has not yet lead to improvements in the care of patients with appetite problems [13, 14, 16]. Only a few studies have investigated appetite from a non-pathophysiological, patient-focused perspective. Studies in diverse patient populations have indicated that psychosocial and medical factors may constitute possible barriers for maintaining appetite [5, 17, 18]. In HF, both cardiac and non-cardiac factors may lead to decreased appetite. Heart failure with fluid overload with bowel edema and breathlessness is likely to cause decreased appetite as patients may feel full, and breathlessness makes it difficult to eat [12, 13, 16]. Moreover, symptoms of depression and sleep disturbances are

common problems in HF populations [19-21], which may also play a role for decreased appetite [22, 23]. Despite appetite being important for maintaining food intake and a healthy weight, there is a lack of knowledge on the significance of problems with decreased appetite in patients with HF. There are no instruments for assessing appetite in HF. In addition, there is a lack of knowledge on the factors that might contribute to decreased appetite and, conversely, whether decreased appetite has an influence on patients' health status.

BACKGROUND

Appetite and nutrition

Nutrition is a basic human need for all life cycles. Food contains important nutrients such as energy, vitamins and minerals that make it possible for the body to build and break down body cells and maintain cellular respiration [24]. Certain organs require more energy than others. For example, the brain consumes about 20% of the total energy intake [24]. Individuals' nutrition intake depends on several factors, where appetite plays an important role [7].

The phenomenon appetite

Appetite is a phenomenon that can be explained by a person's "desire to eat" [25]. There are also other close concepts related to appetite, for example, taste and hunger [7]. Decreased appetite is a common clinical problem in patients with chronic diseases. Various definitions can be used to explain decreased appetite, such as anorexia that in turn are commonly referred to loss of appetite [14, 26-28], reduction/lack of the sensation of hunger or lack of desire to consume food [17, 29], and/or decreased food intake [18, 30]. The drawback with different definitions is that they make it difficult to obtain a comprehensive understanding of the meaning of decreased appetite. Furthermore, few studies detail how appetite has been defined and measured, which further complicates the ability to understand the phenomenon. In this thesis, appetite is defined as the "desire to eat" [26] and the opposite term to appetite is defined as decreased appetite.

Biological regulation of appetite

Appetite is regulated mainly by two systems; the physiobiological systems that refer to processes in the central nervous system (CNS) and the

psychobiological that refer to sensory feeding behaviour [31]. These regulating systems contribute to the body receiving enough nutrients. For example, they regulate food intake when the body is lacking in macro and micronutrients. The body's storage of, for example, energy, fat, glucose and circulating hormones informs the brain about the nutrition status, which in turn leads to a release of hormones that regulate appetite. Any changes in the systems can have a negative impact on appetite and food intake, resulting in poor nutrition outcomes such as overweight or underweight [31].

The sensory systems that collect information about the pleasantness of food, sight, smell, taste and texture transform information to the CNS to stimulate hunger (defined as the motivation to seek food), which prepares the body for ingestion. The regulation for ingestion then passes to the body's physiobiological system. Different receptors of food consumed in the gut and circulating nutrients metabolized in the liver activate the central nervous system to produce metabolic signals that affect satiation, satiety, hunger and fullness, with the aim to downregulate appetite. Thereby, the food circle that is processed by the physiological chain can be seen to be completed [32].

Malnutrition

Nutrition is important for patients with chronic diseases, such as heart failure. Abnormal energy expenditure is problematic in HF, and therefore, nutrition intake is important [33]. Decreased appetite is a clinical problem in HF, which can result in decreased food intake and a number of nutritional disorders, such as malnutrition [12-15]. Approximately 60% of patients with HF are at risk of developing malnutrition, and 13% are defined as malnourished [4]. Nutrition disorders and nutrition related conditions can be grouped in a) malnutrition/synonym with undernutrition b) sarcopenia/frailty c) overweight and obesity d)

micronutrient deficiency, and e) refeeding syndrome. Malnutrition can be defined as “a state resulting from lack of uptake, or intake of nutrition leading to altered body composition (decreased fat free mass) and body cell mass leading to diminished physical and mental function and impaired clinical outcome from disease” [28, p.335]. Furthermore, the etiology for the development of malnutrition can be grouped into disease-related malnutrition with inflammation, disease-related malnutrition without inflammation, or malnutrition without disease [34]. Nutritional concepts have been described in the guidelines by The European Society of Clinical Nutrition and Metabolism [34], as illustrated in Figure 1.

Figure 1. Overview of nutritional disorder and etiology for malnutrition modified by The European Society of Clinical Nutrition and Metabolism guidelines on definitions and terminology of clinical nutrition [34].

Patients with heart failure

Definition, epidemiology, etiology and prognosis

HF is a clinical syndrome in which the heart muscle cannot deliver enough blood to the body, resulting in a cascade of compensatory neurohormonal mechanisms. Hypoperfusion in the kidneys results in the activation of the renin-angiotensin-aldosterone system (RAAS), which in turn leads to high blood pressure via vascular constriction, which stimulates the body to store fluid [35]. This stresses the heart with fluid overload, which results in even more symptom burden. Breathlessness, tiredness and ankle swelling are some clinical and burdensome outcomes [9].

Approximately 26 million people worldwide live with HF. In the United States, Europe and Sweden, the prevalence of HF is estimated to 5.7 million, 15 million and 250 000, respectively [11, 36]. HF affects mainly adult patients, while the prevalence among patients >70 years old is five times higher. Incidence of HF in Sweden 2010 was estimated to 3 per 1 000 inhabitants. The mean age of patients with HF ranges from 70 to 77 years [11, 36] where women are older than men [36]. Ischemic heart disease and hypertension are the most common etiologies for HF. Furthermore, the prognosis is severe; only 50% survive after 5 years [36, 37]. It appears that men's survival rate is five years less to that of women [36].

Heart failure symptoms and comorbidity

The severity of HF symptoms is often measured by the New York Heart Association (NYHA) functional classification (Table 1). This classification is traditionally used as the basis for medical treatment [38]. Heart failure has serious consequences on the patient's social, physical and mental well-being [39-41]. Heart failure symptoms cause burdensome physical limitations that affect the patient's ability to perform basic home routines such as cleaning and washing dishes. The symptom burden causes

emotional stress and frustrations over the life situation, and many patients try to find coping strategies to live as normal a life as possible [41]. The progression of HF is unpredictable. A stable condition can turn into acute deterioration, resulting in the need for acute hospital care [9]. The length of hospital stay ranges between 4 to 20 days and longer hospital stays are associated with a poorer prognosis [11]. Furthermore, both cardiac and non-cardiac comorbidities are great problems associated with poor health outcomes in HF. For example, non-cardiac comorbidities such as malnutrition, chronic obstructive pulmonary disease (COPD) and diabetes may worsen functional capacity [9]. Symptoms of HF and COPD may overlap, which can make it difficult for patients to monitor signs of HF deterioration and decide how to take action and contact health care providers.

Table 1. New York Heart Association (NYHA) functional classification

Classification	Heart failure symptoms
NYHA I	No limitations of physical activity. Ordinary physical activity does not cause undue breathlessness, fatigue, or palpitations.
NYHA II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in undue breathlessness, fatigue, or palpitations.
NYHA III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary physical activity results in undue breathlessness, fatigue, or palpitations.
NYHA IV	Unable to carry on any physical activity without discomfort. Symptoms at rest can be present. If any physical activity is undertaken, discomfort is increased.

Diagnostic criteria and therapy

Patients with symptoms and sign of HF, such as elevated blood samples of natriuretic peptides, may have new onset of HF or deterioration of HF. Blood samples of natriuretic peptides such as B-type natriuretic peptide (BNP) respond normally to fluid overload. BNP (≥ 35 pg/mL) or N-terminal pro BNP (NT-pro BNP) (≥ 125 pg/mL) indicate myocardial stress, which

reflects congestion. Patients that may have new onset HF need to undergo echocardiography for determining heart pumping capacity, i.e., left ventricle ejection fraction (LVEF). LVEF can be grouped in different groups: 1) HF with reduced LVEF <40% (HFrEF), 2) HF with mid-range LVEF 40-49% (HFmrEF), and 3) HF with preserved LVEF $\geq$ 50% (HFpEF). Once the diagnosis has been confirmed, lifelong medical and non- medical treatment aim to reduce symptoms, and improve prognosis and health-related quality of life [9]. Patients with HF with reduced EF should be treated with neurohormonal antagonists, for example, angiotensin-converting enzyme inhibitors (ACE), beta blockers and mineralocorticoid antagonists (MRA). Certain groups of patients may need more advanced treatment including technical devices such as cardiac resynchronization therapy (CRT), an implantable cardioverter-defibrillator (ICD) or mechanical circulatory support and heart transplantation [9].

Non-medical treatment is the other important part of HF management. Patients and preferably family caregivers as well need education about the disease and its progress on, for example, the HF symptoms that are important to pay attention to and manage at an early stage. Patients are advised to regularly vaccinate against influenza and pneumonia as both can result in a deterioration of HF. Nutrition advice focuses on limiting salt intake, while fluid restrictions are necessary for patients with an unexpected gain weight. Patients are also advised to eat healthy food, which should prevent malnutrition [9, 42]. This is a great challenge as decreased appetite is a clinical problem.

Understanding decreased appetite

To date, clinical trials have investigated appetite therapies in patients with cancer [14] and patients with HF [13]. In HF, these studies have not led to improvements in the management of decreased appetite. Heart failure is a symptomatic syndrome and breathlessness and tiredness may have a

negative impact on appetite. The majority of patients with HF are elderly and the ageing process has been shown to negatively impact on appetite hormones [43]. Comorbidity, including symptoms of depression, sleep problems and impaired cognitive function, is a prevalent problem in HF. It has been shown to negatively impact on appetite in general populations, but evidence is limited in HF populations. Physical activity is also an important component in HF management, but the influence of physical activity on appetite is not clearly understood. Medical treatment is crucial to HF management in terms of symptom relief and reducing neurohormonal activation but can may lead to negative consequences for food intake. Many patients with HF also perceive loneliness [44], which may also contribute to an unwillingness to eat [45]. Potential factors for decreased appetite in patients with HF are presented in Figure 2. Current evidence of factors that can potentially be of importance for appetite are described under next paragraph.

Figure 2. Illustration of potential factors for decreased appetite in patients with heart failure.

Factors associated with decreased appetite

In a recent review including 60 articles involving elderly individuals >60 years living in western countries, 100 different correlates to decreased appetite were reported. Seventy-seven physiological and twenty-three non-physiological factors were identified as potential determinants for decreased appetite. Of the non-pathophysiological factors, depression, anxiety and cognition decline were identified as possible contributors for decreased appetite in elderly people. Furthermore, food-related correlates including consistency, temperature and palatability were reported to be other possible correlates. In addition, sociocultural barriers such as social isolation, inability to cook, poverty and environmental factors including living in an institution or one's own home were identified as potential contributors for decreased appetite [18]. These contributors were

suggested to play a role for impaired nutrition status as well. Living alone might be associated with eating fewer meals, resulting in a higher risk of lower BMI compared to those living with others [45]. Furthermore, a cross-sectional study among elderly people over 65 years of age revealed that impaired social support, low income and depression were associated with poor nutrition [46].

Ageing

There is evidence that age related changes in the body affect appetite. A systematic review of 6,208 elderly patients with decreased appetite showed that changes in appetite hormones may vary in elderly people compared to younger individuals. Insulin in which normally respond to carbohydrates that delay gastric emptying and inhibit appetite was found to be higher in elderly compare with younger. In addition, the appetite hormone ghrelin, which is released from the stomach and stimulates appetite, has been shown to be lower in elderly people compared to younger individuals. Elderly people may also have a slower gastric emptying time compared to younger individuals. This might contribute to a sense of fullness, resulting in decreased appetite. Changes in the appetite hormones insulin, glucagon and ghrelin may affect appetite, which can lead to poor food intake and the development of malnutrition [43]. These studies reflect appetite from a physiological point of view where different appetite hormones have been measured.

Depression

Many patients with HF, 42%, are affected by depression. This is a higher figure compared to both general populations and other cardiac populations [19, 20]. Those with depression have a poorer health status compared to those with no depressive symptoms [47]. Depression is furthermore associated with a worse prognosis [20]. Loss of appetite and weight changes are common features in depressive disorders, although the results

are contradicting [22, 23, 48]. One review study showed that a majority of patients with depressive disorders experienced decreases in appetite and weight [48]. Another study of 208 patients with depression aged 21-65 years showed that mild depression may result in better appetite compared to those with more severe depression. This might suggest that increased appetite could be an indicator for the severity of the depressive condition [22]. In contrast, a study of patients with depressive disorder did not find an association between depression and weight, while levels of appetite changed with both increased and decreased appetite. The authors discussed the possibility that some symptoms of depression may result in stress, which in turn may lead to increased appetite. Furthermore, many instruments measuring depressive symptoms contain aspects of appetite that may interfere with the outcome variable appetite. Therefore, appetite-related questions in depressive instruments are considered to be removed. Whether this is an adequate way of dealing with depressive instruments that include appetite is a matter of discussion [23]. A cross-sectional study including 1,694 patients with major depressive disorders found that patients with a higher body mass index (BMI) had better appetite [49]. Depression and appetite has also been investigated in a young group of depressed patients with and without appetite problems. It was found that patients with depression-related increased appetite had greater activity in the reward part of the brain when they saw appetite stimulating pictures compared to those with depression-related decreased appetite [50]. This underlines that the association between depression and appetite is complex. Much of the research on depression and appetite has been performed in younger depressive populations and knowledge on depressive symptoms in relation to appetite in patients with chronic diseases is limited.

In a cross-sectional study among elderly people living in senior and assisted living homes, it was found that mental illness in terms of depression,

hardiness (ability to handle stress) and emotional well-being was significantly associated with appetite. Those with symptoms of depression had more than a two-fold risk of decreased appetite. These results remained significant even after data were adjusted for age [51]. In a small study in patients with end-stage kidney disease, nearly half of the patients reported good appetite and the remaining reported fair and poor appetite. Those with decreased appetite were significantly older and had symptoms of depression [52]. Another study in kidney disease found that patients who scored lower mental health also reported lower appetite [53]. More knowledge are needed in HF populations.

Sleep

Sleep-disordered breathing (SDB) is a common problem in HF, affecting up to 80% of the HF population. It is associated with worsened health outcomes such as morbidity and mortality. The symptoms of SDB may involve disrupted sleep, daytime sleepiness, impaired memory and concentration [54]. Sleep-disordered breathing is more prevalent in HF compared to the general population [21]. The associations between sleep disturbances and appetite are not clearly understood. In a small study among younger participants, it was shown that those with poor sleep quality had changes in appetite hormones. This could lead to an increased food intake, contributing to a larger energy intake [55] that might lead to overweight [56]. These results are based on other populations than HF and therefore more knowledge from a HF perspective is needed.

Cognitive function

Cognitive impairment is a common problem in HF, with a prevalence ranging between 15-46% [57-59]. Studies have shown that patients with HF have a four-folded risk of cognitive impairment compared to healthy populations [57]. Cognitive impairment may affect patients' ability to engage in different tasks, for example, maintaining appropriate self-care

actions such as following medical prescriptions and recognizing and managing a deterioration of HF symptoms [60]. Cognitive impairment may also negatively impact on appetite, which further results in poor nutrition. In an editorial paper, Grundman stated that patients can lose weight several years before they are diagnosed with a cognitive dysfunction such as dementia [61]. The theory for this statement was that patients with cognitive impairments may have a higher prevalence in apathy, irritability, anxiety and depression, which in turn has a negative influence on appetite [61]. A small cohort study in patients with dementia showed that cognitive dysfunction was significantly higher in patients with weight loss and that appetite was evident in body weight loss [62]. Another study showed that cognitive impairment was associated with lower BMI, weight loss and age [63]. The respondents also reported changes both in food habits and decreased appetite. Similar associations were shown in a cross-sectional study, where decreased appetite was associated with low cognitive function in all cognitive domains, including episodic memory, psychomotor function, verbal fluency, and working memory [64]. Cognitive function may also play a role for appetite in patients with chronic diseases. However, only a few studies, among them a cross-sectional study, have found a connection between cognitive function and decreased appetite in patients with kidney disease on dialysis [52]. Studies in diverse patient populations have shown that cognitive function may play a role for nutrition status and appetite, but there is a knowledge gap as to whether cognitive function is associated with decreased appetite in patients with HF.

Physical activity

It is well known that physical activity in patients with HF has positive effects on functional capacity, health-related quality of life and in reducing hospitalizations [9]. However, less than 50% of patients with HF achieve the physical activity goals [65, 66]. To perform physical activity food intake plays an important role. In addition, appetite may be of importance, as food

intake will probably decrease without appetite. It is also likely that there is an opposite direction where physical activity stimulate appetite. Physical activity and appetite has been investigated in different populations and settings. A cross-sectional study showed that frailty was more prevalent in elderly people with decreased appetite compared to those with better appetite [67]. Another study showed that elderly people with decreased appetite were associated with poorer physical function, and that appetite could predict future physical disability [68]. These results were different to those of a study that found that physical activity does not influence appetite [69]. The interplay between physical activity and appetite in patients with HF are not clearly understood.

Assessment of appetite

In clinical practice, different instruments can be used to assess appetite, i.e., the Functional Assessment of Anorexia/Cachexia Therapy (FAACT), the Visual Analog Scale (VAS) [70], and The Appetite, Hunger Feelings, and Sensory Perception (AHSP) [71]. The FAACT instruments were initially designed to assess quality of life and anorexia in patients with cancer and HIV infected patients. It contains 54 items that are self-reported by the patients [72]. Furthermore, the subscale appetite in the FAACT focuses on disease-specific concerns, such as aspects of the person's weight worries, family concerns about eating, vomiting and pain [70]. Thus, it is difficult to apply this instrument to patients with HF, who display other symptoms. The VAS scale can be used to assess self-reported appetite before and after meal tests. Nevertheless, VAS is less accurate for comparing appetite between groups as no statements can be made regarding how large the differences are between individual categories [32]. The AHSP was developed to assess appetite in elderly people. The instrument includes 29 items that focus on appetite, hunger, taste, and smell [71]. In clinical practice, the number of items (29 items) in this instrument may be burdensome for patients with HF to complete. Furthermore, the

instrument has not been validated in patients with chronic diseases such as HF.

There is a lack of validated instruments that measure appetite in patients with HF. This can make it difficult to study appetite and may lead to negative consequences for the patients affected. For example, to date there are no golden standard therapies to improve appetite in HF [14]. One simple self-reported appetite instrument, The Council on Nutrition Appetite Questionnaire (CNAQ), aims to assess appetite in elderly community dwelling populations and has been validated regarding internal consistency reliability and construct validity [7]. The instrument contains a shorter appetite questionnaire, The Simplified Nutritional Appetite Questionnaire (SNAQ). The CNAQ and SNAQ has demonstrated satisfactory validity and reliability. The CNAQ showed moderate correlations with the external appetite questionnaire AHSP which support concurrent validity. Also, internal consistency has been satisfactory [7]. CNAQ and SNAQ could be of special interest to assess appetite in HF as it can be used to predict further weight loss [7]. The instrument is built on few items, which is preferable for use in clinical settings. However, the instrument need to be tested in HF before it can be recommended for clinical use and research.

Caring for patients with decreased appetite

Although medical treatment is lifesaving, the side effects may lead to consequences for food intake. Several of the most important HF medications for example neurohormonal blockade and diuretics may lead to altered taste and smell and reduced saliva production, which in turn may lead to a dry mouth and difficulties to eat and maintain oral health [73]. Interventions, such as serving flavored food, may stimulate saliva production. Furthermore, salt and sour can be used as taste enhancers that stimulate saliva production, although salt restrictions in HF management

make it difficult to provide patients with tasty food. Preferably, patients should be served small portions of their favorite meals with different textures, as saliva production is stimulated by chewing [74]. Even though small interventions may improve saliva production, decreased appetite is rarely a priority in health care settings [26, 75] and it is an unrecognized problem.

Rationale

Malnutrition is a serious condition among patients with HF. It has a negative impact on patients' morbidity, mortality, health and quality of life. Even though the interest in nutrition and food intake has increased in research and clinical practice, few studies have investigated appetite in patients with HF. Appetite plays a central role for food intake, and therefore it is essential that health care professionals assess appetite in order to prevent and delay malnutrition. Currently, there are no validated instruments for assessing appetite in patients with HF. Furthermore, a lack of studies regarding appetite makes it difficult to know how large the problem with decreased appetite is in clinical practice, what factors may influence appetite, and how appetite will change over time. This knowledge is crucial among patients with HF and to identify patients at risk of malnutrition.

AIMS

The overall aim of this thesis was to investigate appetite in patients with heart failure with focus on assessment, prevalence and related factors. The specific aims in the thesis were as follows:

- I To evaluate the psychometric properties of CNAQ and SNAQ in patients with heart failure.
- II To explore the prevalence of decreased appetite and the factors associated with appetite among patients with stable heart failure.
- III To investigate the association between appetite and health status in patients with heart failure, and to explore whether symptoms of depression moderate this association.
- IV To explore the relationship between physical activity, exercise capacity and appetite in patients with heart failure.

METHODS

To capture the complexity of appetite, different study designs and methods were used in this thesis. Four quantitative studies including psychometric evaluation design (I), observation, cross-sectional design (II-III) and observational prospective design (IV) were performed. Data were collected by reviews of medical records, self-reported questionnaires, objective measures and clinical assessments. Research questions and hypotheses were derived from clinical experiences, and previous research, which also guided the methods for data collection. Statistical analyses were guided by research questions. In this thesis, appetite is interpreted as a phenomenon that can be assessed by patients' experiences. An overview of the study methods is presented in Table 2.

Study design and sample

Patients were recruited from three outpatient heart failure clinics in one university and two county hospitals in central Sweden. The inclusion criteria were being verified as having HF assessed by echography or similar methods to verify left ventricle ejection fraction (EF), HF symptoms according to NYHA class II-IV and age ≥ 18 years. Patients on dialysis or with short life expectancy due to other diseases than HF, for example, cancer were excluded. A consecutive sample of 316 patients were invited to participate in the study, of whom $n=186$ (59%) accepted (I-IV) (Figure 3). Non-participants were significantly older than the participants [$t(313)=3.64$, $p<0.001$] but no gender differences were observed ($\chi^2(1)=0.10$, $p=0.701$) (I-IV). Non-participants who declined to participate gave spontaneous explanations to why they declined to participate and notes were documented. Weakness, symptoms of HF and other disease-related obligations such as planned outpatient visits were common explanations.

In total, 116 patients completed the 18-month follow-up study (IV). Seventy patients did not take part in the follow-up due to death or inability to participate due to impaired physical function and other disease-related causes. There were no differences between those who completed the 18-month follow-up and the dropouts regarding gender, age, appetite and physical activity. However, the dropouts had significantly higher NYHA class at baseline ($\chi^2(2)=12.7$, $p=0.002$).

Figure 3. Overview of the recruitment of patients at baseline and at the 18-month follow-up.

Table 2. Overview of the methods in the thesis (I-IV)

	Study I	Study II	Study III	Study IV
Design	Psychometric evaluation	Observational, cross-sectional	Observational, cross-sectional	Observational, prospective
Participants	Baseline: outpatients with HF, NYHA class II-IV, age ≥ 18 y (n=186)	Baseline: outpatients with HF, NYHA class II-IV, age ≥ 18 y (n=186)	Baseline: outpatients with HF, NYHA class II-IV, age ≥ 18 y (n=186)	Baseline: outpatients with HF, NYHA class II-IV, age ≥ 18 y (n=186) Follow-up: (n=116)
Data source	Questionnaires Clinical data Objective data Medical records	Questionnaires Clinical data Objective data Medical records	Questionnaires Clinical data Objective data Medical records	Questionnaires Clinical data Objective data Medical records
Predictor variable	N/A	Gender, age, cohabitation, NYHA, comorbidity, BNP, symptoms of depression, health status, sleep, cognitive function, medical treatment	Appetite Symptoms of depression (moderator)	Physical activity Exercise capacity
Outcome variable	Appetite	Appetite	Health status	Appetite
Analysis	Polychoric/polyserial correlations Factor analysis Spearman's rho coefficient Mann-Whitney U test Ordinal coefficient alpha	Spearman's rho coefficient Multiple and robust linear regression	Pearson correlation Multiple linear regression Moderation analysis	Pearson correlation Simple linear regression Paired sample t-test

BNP, B-type natriuretic peptide; NYHA, New York Heart Association (NYHA) functional classification; HF, heart failure

Sample size

A priori sample size was calculated for study II-IV. The sample calculations were based on the planned analysis and general recommendations. The sample size for study II-IV were based on Cohen's general recommendations for multiple linear regression analysis [76, 77]. Using these guidelines, a minimum required sample size was estimated to 117, based on the following criteria; a medium effect size ($f^2=0.15$), 10 explanatory variables (estimated), $\alpha=0.05$ and $1-\beta=0.80$. In addition, separate power analyses were conducted for each study respectively.

Procedure and data collection

Research nurses at the HF clinics informed patients about the study and its contents at a regular outpatient HF appointment. Patients who were interested to participate in the study received oral and written information about the contents of the study and the requirements including questionnaires, objective and clinical assessments and visit procedures. Patients were informed that they could drop out of the study without any negative effects on their usual HF care. One week after the regular HF appointment, research nurses from the respective study site contacted the patients scheduled a meeting. A study protocol ensured that data were collected equally at the three study sites.

Two visits were scheduled within a week. The first visit took place at the hospital and the second at the hospital or in the patients' homes depending on the patients' preferences. At the first meeting at the hospital, data collection included medical records (pharmacological treatment, comorbidity, left ventricle ejection fraction, time of diagnosis), clinical data (NYHA class), objective data (anthropometric assessment of body size, blood samples, six minutes' walk test. An actigraph (SenseWear®) to assess physical activity and a questionnaire (demographic background

data, appetite, symptoms of depression, health status, sleep, self-reported physical activity) were also handed out to be completed at home. After one week, the actigraph and the questionnaires were returned, and a cognitive test was performed at the hospital or in the patients' homes. For the 18-month follow-up study, patients were contacted by the research nurses and the same procedure were followed as at baseline.

Variables and instruments

Data were collected from medical records (pharmacological treatment, comorbidity, left ventricle ejection fraction, time of diagnosis), self-reported questionnaires (demographic background data, appetite, symptoms of depression, health status, sleep, self-reported physical activity), objective measurements (anthropometric assessment of body size, blood samples, six minutes' walk test, and physical activity measured with an actigraph) and clinical assessment (New York Heart Association (NYHA) functional classification, and cognitive assessment). The self-reported instruments for the studies in the thesis are presented in Table 3.

Table 3. Overview of self-reported instruments in study I-IV

Study	Measures	Instruments	Abbreviations
I	Appetite	Council of Nutritional Appetite Questionnaire	CNAQ
	Symptoms of depression	Patient Health Questionnaire	PHQ-9
II	Appetite	Council of Nutritional Appetite Questionnaire	CNAQ
	Symptoms of depression	Patient Health Questionnaire	PHQ-9
	Daytime sleepiness	The Epworth Sleepiness Scale	ESS
	Insomnia	The Minimal Insomnia Symptom Scale	MISS
	Health status	European Quality of Life-5 Dimensions	EQ-5D
III	Appetite	Council of Nutritional Appetite Questionnaire	CNAQ
	Symptoms of depression	Patient Health Questionnaire	PHQ-9
	Health status	European Quality of Life-5 Dimensions	EQ-5D
IV	Appetite	Council of Nutritional Appetite Questionnaire	CNAQ
	Physical activity	Physical activity assessed by Numeric Rating Scale	NRS

Appetite was measured with the Council of Nutrition Appetite Questionnaire (CNAQ). The instrument was developed to measure self-reported appetite in community-dwelling adults and contains eight items; 1=appetite, 2=saturation, 3=hunger, 4=food taste, 5=taste compared to younger age, 6=amount of food intake, 7=nausea and 8=mood, see Appendix. Each item has five response options, coded from 1-5, that are summed into a total score ranging from 8-40. High total scores indicate a high level of appetite [7]. A cut-off value can be used, a CNAQ score ≤ 28 indicates decreased appetite with a significant risk of weight loss over a 6-month period. A short version of CNAQ, i.e., the Simplified Nutritional Appetite Questionnaire (SNAQ,) includes four items; 1=appetite, 2=saturation, 4=food taste and 6=amount of food intake. A cut off of ≤ 14 for the SNAQ indicates risk of weight loss over a 6-month period [7]. The CNAQ has not been used or been validated in patients with HF in Sweden. Thus, a cross culture translation from English to Swedish was performed,

inspired by the WHO criteria for translating and adapting instruments [78]. An independent native Swedish translator with English language skills translated the instrument into Swedish. Thereafter, a native English translator with Swedish language skills translated the instrument back into English. The retranslated English version was then compared with the original version and on that basis, minor adjustments were made in the Swedish version. In this thesis, the scale has been used both as continuous scale and the recommended cut-off [7].

Symptoms of depression were measured with the Patient Health Questionnaire (PHQ-9). This self-reported validated instrument contains nine items about bothersome symptoms of depression over the last two weeks. Each item is responded to on a numeric scale with four response options; 0=not at all, 1=several days, 2=more than half the day, 3=nearly every day. The total score ranges between 0-27 and can be categorized to identify severity of the symptoms of depression; 0-4=no symptoms of depression, 5-9=mild symptoms of depression, 10-14=moderate symptoms of depression, 15-19=moderately severe and 20-27=severe symptoms of depression [79]. PHQ-9 has been validated and has demonstrated acceptable psychometric properties in patients with HF [80]. In this thesis the scale was used as a continuous and a dichotomized scale. The internal consistency in this thesis was acceptable, estimated with Cronbach's alfa ($\alpha=0.80$).

Daytime sleepiness was measured by the Epworth Sleepiness Scale (ESS). Eight items reflect the chances that a person would doze off in different situations; sitting and reading, watching TV, sitting inactive in a public area, as a passenger in a car, in a car while stopped for traffic, lying down, sitting and talking, sitting after lunch. Subjects report daytime sleepiness on a Likert-type scale; 0=would never doze, 1=slight chance of dozing, 2=moderate chance of dozing and 3= high chance of dozing. The total score

is 24 and a score of 16 or greater indicates a high level of daytime sleepiness [81]. ESS has been validated in general adult populations, but not in HF populations [82]. In this thesis, the scale was used as a continuous scale. The internal consistency was acceptable, estimated with Cronbach's alfa ($\alpha=0.75$).

Sleeping difficulties was measured by the screening instrument Minimal Insomnia Symptom Scale (MISS). This three-item instrument was used to measure insomnia based on questions about difficulties falling asleep at night, night awakenings, and not feeling rested by sleep. Participants were asked to report their sleep difficulties on a five- point Likert-type scale, where a low score (0) indicates no problems and a high score (4) indicates severe problems. The total score ranges from 0-12, and a cut- off value of ≥ 6 can be used to identify persons with sleep problems [83]. The instrument has shown sound psychometric properties among adults and elderly populations [84] but has not been validated in HF. In this thesis, the scale was used as a continuous scale. The instrument's internal consistency in this thesis was acceptable, estimated with Cronbach's alfa ($\alpha=0.80$).

Cognitive function was measured by the Minimal Mental State Examination (MMSE). This instrument is primarily used to assess cognitive impairment and not for diagnostic purposes. It covers cognitive functions, including orientation, registration, attention, calculation, recall and language and is answered verbally. The maximum score is 30, scores ranging between 24-30 indicate no cognitive impairment, whereas scores <24 indicate mild to severe cognitive impairment [85]. The instrument has been recommended by the European Society of Cardiology (ESC) for assessing cognitive function in patients with HF [9].

Physical activity was measured by a numeric rating scale (NRS) ranging from 1-10. Participants were instructed to report their current physical activity in terms of daily housework and leisure time activities such as walking and cycling. Lower scores indicated lower levels of physical activity. In addition, physical activity was measured by a validated multi-sensor wearable actigraph (SenseWear®, Body Monitoring System) [86]. The patients were instructed to wear the actigraph for seven days. Four sensors detected skin temperature, galvanic skin response, heat flux sensor and two axis accelerometer. These data were processed and calculated by algorithms and presented in four physical activities areas; total energy expenditure (TEE), active energy expenditure (AEE) above 3 METs (Metabolic Equivalent Unit), and number of steps. METs are used to indicate individuals' energy consumption related to specific physical activities (resting consumption=1 METs=1 kcal/kg/hour). Resting energy expenditure is calculated by a formula, for example, a 70 kg subject has a resting energy expenditure of 1 MET x 70 kg x 24 hours = 1680 kcal/day). The METs daily average was used as a measure of physical lifestyle; 1.2-1.3=sedentary/inactive, 1.4-1.6=normal and >7=active [86].

Health status was measured with the European Quality of Life-5 Dimensions three- level version (EQ-5D-3L) which is a standardized, generic and specific self-reported instrument. EQ-5D-3L measures health status in five different dimensions; mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each health dimension has three response levels; 1=no problems, 2=some problems, and 3=extreme problems. According to a scoring algorithm, the five items are compiled into a health index, the EQ-5D-3L index, which ranges between -0.59 and 1, corresponding to worst and best health status respectively. EQ VAS measures health status on a VAS scale ranging from 0-100, where high scores indicate the best possible health [87, 88]. Validation studies on EQ-

5D-3L have shown adequate psychometric properties in cardiac populations [89-91].

Cardiac stress, functional capacity and anthropometrics

Cardiac stress was assessed by blood samples B type natriuretic peptide (BNP). This peptide increases as a result of fluid retention and can guide the HF treatment. BNP levels of ≥ 35 picogram per milliliter (pg/mL) indicate fluid retention and possibly deterioration of HF symptoms [9]. A six minute's walking test was conducted to determine general functional exercise capacity [92] and to determine NYHA class [93]. Participants were instructed to walk back and forth indoor, along a 30 meter corridor, as rapidly as possible under six minutes. If any symptoms of breathlessness, fatigue or palpitations occurred, participants were advised to slow down to be as comfortable as possible or terminate [92]. The distance is measured in meters and a walking distance < 350 meters is associated with impaired functional capacity and worsened HF prognosis [92]. Anthropometric measures were performed by measuring length and weight and by ratio between these, the Body Mass Index (BMI). BMI is calculated as weight (kg)/height (m^2). According to WHO classifications for people ≥ 65 years, BMI < 18.5 is classified as underweight, BMI 18.5-24.99 is as normal weight, BMI 25.00 to 29.99 with as overweight and BMI ≥ 30 as obese [94]. BMI can be used to determine nutrition status. BMI < 20 in subjects < 70 or BMI < 22 in subjects 70 years of age indicates a risk of developing malnutrition [28]. Participants' weight and height were measured with indoor clothes, empty pockets and without shoes. The waist-hip ratio (waist circumference divided by hip circumference) was measured to estimate abdominal fat. A waist-hip ratio of ≥ 0.90 cm for men and ≥ 0.85 cm for women indicates an increased risk of developing metabolic complications [95]. These measures are associated with BMI, i.e., a higher waist-hip ratio is considered with higher BMI [94].

Data analysis

General statistical analysis

Both parametric and non-parametric statistical analyses were used depending on data level and distribution of data. Descriptive statistics were used to describe sample and study variables. *Categorical* variables are presented as numbers with percentage while *continuous* variables are presented as mean with standard deviation (SD) or median with interquartile range (IQR). Additionally, to compare characteristics between participants, data were analyzed with Pearson Chi-square test, Mann-Whitney U test and/or independent sample t-test [96]. A p-value <0.05 was considered as statistically significant in the thesis. General statistical data analysis in this thesis were conducted by using IBM SPSS Statistics version 20.0 (IBM Corp, Armonk, NY, USA).

Specific statistical analysis

Study I

In order to evaluate the psychometric properties of the appetite questionnaire CNAQ and the short version SNAQ 1) data quality, 2) item homogeneity, 3) factor structure, 4) construct validity, 5) known-group validity, and 6) internal consistency were evaluated. Items were treated as ordered categories in all analyses. *Data quality* was evaluated by the distribution of item and scale scores to detect possible problems with ceiling and floor effects, i.e., the proportion of minimum and maximum scores [97]. *Homogeneity* of the items was evaluated with inter-item correlations and item-total correlations, based on polychoric and polyserial correlations (ρ), respectively. Item-total correlation was considered acceptable to $\rho > 0.3$ [98].

Factor analysis was used to evaluate if CNAQ was a unidimensional measure of appetite. In the first step, a parallel analysis was performed to evaluate if a one-factor model was the most appropriate. Based on these

findings, confirmatory factor analyses (CFA) were conducted. The items were treated as ordinal variables, and parameters were estimated by a robust weighted least squares estimator using a diagonal weight matrix (WLSMV) [99]. Different goodness of fit indices were used to evaluate the fit between model and data. For a perfect fit, the following criteria were used; a non-significant χ^2 test, RMSEA (Root Mean Square Error of Approximation) ≤ 0.06 , CFI (Comparative Fit Index) ≥ 0.95 , TLI (Tucker-Lewis Index) ≥ 0.95 [100] and WRMR (Weighted Root Mean Square Residual) < 1.0 [101].

According to construct validity, the associations between the CNAQ and SNAQ and symptoms of depression were evaluated by using the Spearman rho coefficient (r_s). Based on previous studies showing that depression correlate with appetite, the hypothesis was that patients with lower levels of appetite should report higher levels of symptoms of depression ($r_s \geq 0.30$). No strong correlations were expected ($r_s \geq 0.90$) as these concepts do not measure the same constructs as the CNAQ.

Known-group validity was evaluated by comparing the CNAQ and the SNAQ scores between patients with mild HF symptoms (NYHA II) and moderate to severe HF symptoms (NYHA III and IV), using the Mann-Whitney U test. As symptoms of HF may correlate with appetite, it was hypothesized that patients with moderate to severe symptoms would score significantly lower levels of appetite compared to patients with mild HF symptoms.

The ordinal coefficient alpha was calculated to evaluate the internal consistency. Ordinal alpha of 0.7 or greater was considered sufficient to support internal consistency [102].

Specific data analyses for study I were conducted by using IBM SPSS Statistics version 20.0 (IBM Corp, Armonk, NY, USA), Stata 14.0 (Statacorp, College Station, Texas), Factor 9.2 (Rovira I Virgili University, Tarragona, Spain), Mplus 7.3 (Muthen and Muthen, Los Angeles, California).

Study II

Prevalence of decreased appetite was investigated by using CNAQ as a dichotomized variable, low ≤ 28 respective high > 28 appetite. To explore possible predictors for appetite (gender, age, cohabitation, NYHA class, comorbidity, myocardial stress, symptoms of depression, self-perceived health, sleep, cognitive function and pharmacological treatment) Spearman's rank correlation coefficient (r_s) was used. Predictors that were significantly correlated with appetite were further explored in a multiple linear regression analysis with a stepwise procedure with backward elimination. This means that all variables in the model are added and then the least significant variable is dropped as long as it is not significant according to the chosen significance level. The data analysis was conducted by using IBM SPSS Statistics version 20.0 (IBM Corp, Armonk, NY, USA) and Stata 14.0 (Statacorp, College Station, Texas).

Study III

Pearson correlation (r) was used to investigate the association between appetite (CNAQ) and health status (EQ-5D-3L). To explore whether symptoms of depression moderate the associations between appetite and health status, a multiple linear regression analysis was conducted in four blocks. A moderation occurs when the relationship between a predictor variable and outcome variable changes because of the moderator. A moderation effect is identified when there is a statistical significance of the moderator [103]. Appetite (CNAQ) was treated as a continuous variable and symptoms of depression (PHQ-9) was dichotomized into two groups,

none to minimal symptoms of depression (1-4) and mild to severe symptoms of depression (5-27). Health status (EQ-5D Index) and (EQ VAS) were treated as outcome variables, whereas appetite, symptoms of depression were treated as predictor variables. Appetite was included as a single predictor variable in block I and symptoms of depression were added in block II. In the third block, the interaction term (i.e, moderator) between appetite and symptoms of depression were added to evaluate the moderation effect of symptoms of depression. Finally, the models were adjusted for age, gender and NYHA class in block IV because these variables have been found to be important for appetite and health status.

A significant association between the interaction term and health status (block III) was considered to progress the analysis further with simple sloop analyses. The aim of these analyses were to explore if the association between appetite and health status was equal in patients with and without symptoms of depression. Specific analyses of the simple slopes of the association between appetite and health status in participants with none to minimal symptoms of depression ($\text{PHQ-9} \leq 4$), and mild to severe symptoms of depression ($\text{PHQ-9} > 4$), were performed by using a specific online program for moderation analyses [104].

Study IV

Pearson correlation and simple linear regression analyses were used to explore the association between physical activity, exercise capacity and appetite. The predictor variables from baseline consisted of self-reported physical activity, total energy expenditure, active energy expenditure above 3 METs, METs daily average, number of steps per day and six minutes' walk test, while appetite (CNAQ) from baseline was used as outcome variable. Study patients were instructed to wear the multi-sensor wearable actigraph (SenseWear®) for seven days. All patient had valid data for four days and a daily mean was calculated from that. To explore whether physical activity

and exercise capacity predicted appetite at the 18-month follow-up, simple regression analyses were repeated with the same physical activity and exercise predictor variables from baseline assessment while appetite (CNAQ) was taken from the 18-month follow-up assessment. In order to explore changes in physical activity, exercise capacity and appetite over time, paired t-tests were used [103].

Ethical considerations

This thesis was conducted according to ethical principles of the World Medical Association Declaration of Helsinki [105]. Ethical approval for research involving human participants was obtained by the Regional Ethical Review Board, Linköping, Sweden (No. M222-08/T81-09). According to information requirements in human research, patients were given both oral and written study information. Participation was solely voluntarily, and participants could withdraw at any time during the study. Furthermore, study participants gave their informed consent before entering the study. Data materials were treated confidentially and labelled with study codes to ensure that the participants' responses could not be linked to their identity. Only the investigator could connect the responses to the individual subjects. The codes were stored and handled with caution in a secure room, separately from the data materials. To fulfill the requirement of usefulness of sources, data were kept to be used for solely the research project.

Protecting participants from harm and discomfort due to their actual health status was also a priority. In this thesis, data collection was based on non-invasive measurements, except blood samples. Filling in the questionnaire poses a minor risk of physical harm, but can be perceived as bothersome in relation to psychosocial factors. Especially the data collection in relation to cognitive function and symptoms of depression were handled with care. There was a multiprofessional preparedness to

handle potential deviations related to the data collection. The invasive methods consisted of blood samples as these may be perceived as unpleasant. Before blood sampling, the participants were resting on a bed and they had the option of a local analgesic. Special needles were used for those with small and weak vessels to reduce the risk of hematoma. Clinical and objective assessments were conducted, based on protocols. The participants were interviewed about HF symptoms and circulatory parameters were controlled to avoid exposing anyone to the risk of falling. Potential risks for the participants were weighted against the benefits of the study.

RESULTS

In this thesis, 186 patients with HF participated (I-IV). Of these, 116 participated in the 18-month follow-up (IV). Mean age at baseline was 70.7 years (SD=11.0). Most of the participants had mild to moderate HF symptoms, corresponding to NYHA class II and III, and were treated with conventional HF medications according to HF guidelines. An overview of descriptive and sample characteristics is presented in Table 4.

Table 4. Demographic and HF characteristics at baseline and 18-month follow-up

Measures	Baseline (n=186)	Follow-up (n=116)
Age, mean (SD)	71 (11)	72 (11)
Gender, n (%)		
Female	56 (30)	40 (34)
Male	130 (70)	76 (66)
Cohabitation, n (%)		
Yes	124 (67)	74 (64)
No	62 (33)	42 (36)
NYHA class, n (%)		
II	114 (61)	78 (67)
III	60 (32)	35 (30)
IV	12 (6)	3 (3)
LVEF, n (%)		
40-49	47 (25)	46 (40)
30-39	76 (41)	38 (33)
<30	63 (34)	32 (27)
BNP (pmol/L), mean (SD)	189 (195)	140 (159)
BMI (kg/m ²), mean (SD)	29 (5)	28 (5)
CCI, mean (SD)	1.8 (1.2)	1.9 (1.1)
Pharmacological treatment, n (%)		
Beta blocker	174 (94)	107 (92)
ACE-Inhibitor	111 (60)	67 (58)
Angiotensin receptor blocker	76 (41)	49 (42)
Mineralocorticoid antagonist	63 (34)	49 (42)
Appetite		
CNAQ ≤28, n (%)	71 (38)	49 (42)
CNAQ >28, n (%)	115 (62)	67 (58)

NYHA class, New York Heart Association (NYHA) functional classification; LVEF, Left Ventricular Ejection Fraction; BNP, B-type natriuretic peptide; BMI, Body mass Index; CCI, Charlson Comorbidity Index; CNAQ, Council on Nutrition Appetite Questionnaire

Psychometric evaluation of CNAQ and SNAQ

The evaluation of the appetite instrument CNAQ showed no missing data in any of the items (I). Most of the ratings on the five-point response scale were centered to the middle and slightly above the middle of the scale. The first response category for items 1, 4 and 6 was not endorsed by any of the patients. No problems with floor effects were revealed, except for item 7 which showed a ceiling effect with 69.9% endorsing the highest response category (Table 5).

Table 5. Item score distributions, n (%) for CNAQ and SNAQ (n=186). Item responses are scored on a five-point verbal scale I-IV, where lower scores indicate a low level of appetite

Items	Median (q1-q3)	I	II	III	IV	V
1*	4 (3-4)	-	11 (5.9)	45 (24.2)	101 (54.3)	29 (15.6)
2*	4 (4-4)	3 (1.6)	3 (1.6)	33 (17.7)	140 (75.3)	7 (3.8)
3	3 (2-3)	19 (10.2)	51 (27.4)	101 (54.3)	14 (7.5)	1 (0.5)
4*	4 (4-4)	-	2 (1.1)	22 (11.8)	121 (65.1)	41 (22.0)
5	3 (3-3)	2 (1.1)	29 (15.6)	120 (64.5)	27 (14.5)	8 (4.3)
6*	3 (3-4)	-	29 (15.6)	67 (36.0)	76 (40.9)	14 (7.5)
7	5 (4-5)	1 (0.5)	4 (2.2)	23 (12.4)	28 (15.1)	130 (69.9)
8	4 (3-4)	1 (0.5)	6 (3.2)	81 (43.5)	94 (50.5)	4 (2.2)
CNAQ	30 (27-31)					
*SNAQ	15 (14-16)					

CNAQ (Council on Nutrition Appetite Questionnaire) items =1-8 (possible range 8-40)

SNAQ (Simplified Nutritional Appetite Questionnaire) items =1, 2, 4, 6 (possible range 4-20)

Inter-item and item-total correlations were found to be generally satisfactory and supported homogeneity (I). The inter-item correlations ranged between 0.013 and 0.697 for CNAQ, and 0.274 and 0.697 for SNAQ. The item-total correlation for CNAQ was acceptable, except for item 6 “Normally I eat...”, and item 8 “Most of the time my mood is...”, which were slightly lower than the acceptable level ($\rho > 0.3$), 0.267 and 0.273 respectively. Item-total correlations for the other items in CNAQ ranged

between 0.323 and 0.758. Item-total correlations for SNAQ all exceeded the level of >0.3 , ranging between 0.349 and 0.627 (Table 6).

Table 6. Inter-item (polychoric rho) and item-total correlations (polyserial rho) for CNAQ and SNAQ (n=186)

Items	1	2	3	4	5	6	7	8	Item-total correlations ^a	
									CNAQ	SNAQ
1*	1.000								0.758	0.603
2*	0.595	1.000							0.571	0.517
3	0.424	0.382	1.000						0.323	-
4*	0.697	0.454	0.195	1.000					0.671	0.627
5	0.526	0.503	0.307	0.591	1.000				0.574	-
6*	0.290	0.273	0.068	0.349	0.080	1.000			0.267	0.349
7	0.611	0.526	0.164	0.490	0.457	0.214	1.000		0.494	-
8	0.421	0.013	0.122	0.302	0.312	0.065	0.124	1.000	0.273	-

^a Acceptable to rho >0.3

CNAQ (Council on Nutrition Appetite Questionnaire) items=1-8

*SNAQ (Simplified Nutritional Appetite Questionnaire) items=1, 2, 4 & 6

Regarding factor structure, a one-factor solution for both CNAQ and SNAQ was supported by the parallel analysis. Eigenvalues based on parallel analysis of CNAQ were 3.16 for the first factor and 0.33 for the second factor. For SNAQ, the eigenvalues were 1.96 for the first factor and 0.08 for the second factor. Based on these findings, a one-factor CFA solution was considered in the following evaluations of factor structure.

The baseline model of CNAQ (the first model without any modifications) deviated significantly from data according to the χ^2 goodness-of-fit statistics. In addition, RMSEA was higher than expected (>0.06). However, the confidence interval for RMSEA covered this critical value. Both CFI and TLI were above the critical value of 0.95, and WRMR was below the critical value of 1.0, as expected for a good model fit. As the patients rarely endorsed the first response category, the first and second response categories were collapsed for all items in the second model. This improved the model fit somewhat, but the χ^2 goodness-of-fit statistics were still

significant and the RMSEA value was still above 0.06. By collapsing these response categories, CFI, TLI, and WRMR also improved. As item 8 “Most of the time my mood is...” conceptually measures mood rather than appetite, the residual variance for this item was allowed to correlate with item 2 in the third model, based on the modification index. This minor modification improved the model significantly and all criteria for a good model fit were fulfilled. The SNAQ baseline model showed acceptable model fit without any modifications. All factor loadings in all three models were significant at a level of $p < 0.001$. Item 1 showed the strongest factor loadings in all three models, while item 6 showed the weakest factor loadings (Figure 4).

A further analysis of construct validity showed that appetite was significantly associated with symptoms of depression as hypothesized. For CNAQ, higher level of symptoms of depression correlated significantly with lower level of appetite $r_s = -0.422$, $p < 0.001$. Similar findings were demonstrated for SNAQ $r_s = -0.383$, $p < 0.001$. The construct validity of the CNAQ scale was also confirmed by analysis of known-group validity, which showed that appetite levels were significantly lower in patients with severe heart failure symptoms (NYHA III and IV), compared to patients with less symptoms (NYHA II) (Δ median=2, $p = 0.002$). A similar finding was demonstrated for SNAQ (Δ median=1, $p = 0.006$).

Ordinal alpha supported internal consistency reliability for both CNAQ (0.82) and SNAQ (0.77).

Figure 4. Presentation of the final confirmatory factor models of the CNAQ (model with collapsed response options and correlated errors for item 2 and 8) and SNAQ (unadjusted model). All factor loadings (SNAQ within brackets) were significant at a level of $p < 0.001$. Goodness-of-fit indices for CNAQ: $\text{RMSA} = 0.05$, $\text{CFI} = 0.99$, $\text{TLI} = 0.98$, $\text{WRMR} = 0.61$, $\text{CI} = 0.00\text{--}0.09$, $p\text{-value} = 0.443$. Goodness-of-fit indices for SNAQ: $\text{RMSA} = 0.05$, $\text{CFI} = 1.0$, $\text{TLI} = 0.99$, $\text{WRMR} = 0.30$, $\text{CI} = 0.00\text{--}0.16$, $p\text{-value} = 0.368$.

Recommended levels for acceptable model fit: Root mean Square error of Approximation ($\text{RMSA} \leq 0.06$), Comparative Fit Index ($\text{CFI} \geq 0.95$), Tucker Lewis Index ($\text{TLI} \geq 0.95$), Weighted Root Square Residual ($\text{WRMR} \leq 1.00$), $p\text{-value} (> 0.05)$.

Prevalence of appetite problems in heart failure

Based on CNAQ, it was found that as many as 38% (n=71) of the participants had an appetite level at risk for future weight loss. Using SNAQ, 31% (n=57) had an appetite level at risk for future weight loss (II).

Factors associated with decreased appetite

Several factors were shown to be associated with appetite measured by CNAQ. The bivariate correlation in study II showed that nine out of thirteen predictors were significantly associated with appetite; older age ($r_s = -0.204$, $p = 0.005$), living alone ($r_s = 0.194$, $p = 0.008$), higher NYHA class ($r_s = -0.237$, $p = 0.001$), impaired self-perceived health status including EQ-5D ($r_s = 0.389$, $p < 0.001$) and EQ VAS ($r_s = 0.320$, $p < 0.001$), higher level of depression ($r_s = -0.442$, $p < 0.001$), insomnia ($r_s = -0.390$, $p < 0.001$), impaired cognitive function ($r_s = -0.251$, $p = 0.001$), and medical HF treatment ($r_s = 0.158$, $p = 0.032$). The four remaining predictors; gender, comorbidity, myocardial stress, and daytime sleepiness did not show any significant associations with appetite. To further explore the relationship between the predictors and appetite, a stepwise multiple regression analysis showed that older age ($B = -0.05$, $p = 0.015$), higher level of depression ($B = -0.22$, $p = 0.001$), insomnia ($B = -0.22$, $p = 0.015$), impaired cognitive function ($B = 0.25$, $p = 0.007$), and insufficient medical HF treatment ($B = 1.18$, $p = 0.021$) independently were associated with lower levels of appetite, while living with someone, NYHA class and self-perceived health were not significantly associated with appetite.

Regarding the relationship between physical activity, exercise capacity and appetite, study IV showed significant associations between objective physical activity variables, including total energy expenditure ($B = 0.0001$, $p = 0.041$), active energy expenditure ($B = 0.0020$, $p = 0.017$), number of steps ($B = 0.0003$, $p < 0.001$), METs daily average index ($B = 3.422$,

$p=0.007$), six minutes' walk test ($B=0.0059$, $p=0.001$), and appetite at baseline. Higher levels of physical activity were associated with higher levels of appetite. There were no associations between self-reported physical activity and appetite at baseline ($B=0.2803$, $p=0.057$).

Further, higher levels of physical activity at baseline predicted higher levels of appetite at the 18-month follow-up. All physical activity variables predicted appetite at the 18-month follow-up, including total energy expenditure ($B=0.0012$, $p=0.035$), active energy expenditure ($B=0.0025$, $p=0.018$), number of steps ($B=0.0003$, $p<0.001$), METs daily average index ($B=4.163$, $p=0.003$), six minutes' walk test ($B=0.0054$, $p=0.010$) and self-reported physical activity ($B=0.3733$, $p=0.026$).

Changes in physical activity and appetite over time

Study IV showed that either physical activity (self-reported physical activity, total energy expenditure, active energy expenditure, METs daily average index, six minutes' walk test) or appetite measured by CNAQ changed between baseline and the 18-month follow-up ($p=0.054-0.830$).

Appetite and health status

Overall, study III showed that higher levels of appetite, measured by CNAQ, were associated with better health status. Appetite was significantly associated with mobility function ($r=-0.26$, $p<0.001$), pain/discomfort ($r=-0.31$, $p<0.001$) and anxiety/depression ($r=-0.24$, $p<0.001$) (III). However, it was not associated with self-care or usual activities. Furthermore, a significant relationship between appetite and health status was shown, measured with the EQ-5D-3L index ($r=0.37$, $p<0.001$) and EQ VAS ($r=0.38$, $p<0.001$).

Moderation effect of depression

The association between appetite and health status, measured with the EQ-5D-3L index, was moderated by symptoms of depression (III). This was evident throughout the four regression blocks, including appetite, depression, a multiplicative interaction term of appetite and depression, and the covariates age, gender and NYHA classification. A simple slope analysis showed that a relationship between appetite and health status was evident in participants with no to minimal symptoms of depression ($B=0.32$, $p < 0.001$), but not for patients with mild to severe symptoms of depression ($B=0.01$, $p=0.290$). No moderation effect was found for health status measured with EQ VAS when the interaction term appetite and depression was entered the model.

DISCUSSION

Discussion of the results

The present thesis contributes with new knowledge about appetite in patients with HF. The CNAQ showed acceptable psychometric properties for use in clinical practice and research. A large share of the patients reported decreased appetite and it was evident that patient demographic and clinical characteristics, and psychological and physical factors were associated with decreased appetite. Furthermore, appetite had an impact on health status, but only in patients with absence of symptoms of depression.

Tools to assess appetite in heart failure

Overall, the appetite instrument CNAQ showed sound psychometric properties regarding construct validity and internal consistency in patients with HF (I). Although the construct validity of the factor structure, i.e., the items covered, one underlying construct, the factor loadings for item 6 (food intake), was somewhat weak. One explanation could be that food intake reflects more objective values on the number of meals eaten per day compared to items that reflect experiences and feelings. Moreover, in line with other studies [7, 106], the item about taste showed high factor loadings, which indicates that taste is an important factor for appetite. Furthermore, the CNAQ contain one item about mental health and PHQ-9 contains one item of appetite and they might overlaps. This is a problem and not easy to solve. For psychometric adequacy, items should preferably not be removed from a developed instrument.

As hypothesized, symptoms of depression and disease severity supported the construct validity, implying that patients with higher levels of

depression and more HF symptoms experience lower appetite. At this stage, the CNAQ can be used to assess appetite in patients with HF. However, to identify patients with HF at risk of weight loss and malnutrition, the instrument's predictive value needs to be further explored.

Prevalence and factors for decreased appetite

The prevalence of appetite levels at risk of weight loss (II) was much higher (38%) compared to the 8% reported in a small group of hospitalized elderly patients with HF [107]. It was also somewhat higher compared to studies on kidney disease (24-27%) [108, 109]. The study patients in this thesis were older and recruited from outpatient clinics, compared to those who were admitted to hospital [107]. Despite this, more patients had problems with appetite in the sample from this thesis (II). One possible explanation is that different instruments have been used to identify appetite such single item with different response options i.e., categorized, Likert scale and VAS scale [107-109]. This can also explain why patients with kidney disease reported less problems with appetite [108, 109] compared to the patients with HF in this thesis. However, it is difficult to compare patients with a different diagnosis, such as kidney disease and HF as the symptoms differ.

As appetite problems seem to be common in patients with HF (II), and may serve as a prognostic factor for malnutrition [26] and worsen prognosis in chronic diseases [110], assessing appetite is an important task in clinical practice. Currently, there is no treatment to improve appetite in HF. It is therefore important to focus on nursing interventions that guide patients to optimize their nutrition intake according recommendations for healthy individuals. Small, more frequent meals and energy dense meals are of importance [111]. Also, as many of the cardiac medications include ACE-inhibitors and diuretics may contribute to altered taste which in turn can have negatively effect on appetite health care can make patients aware of

that taste can be stimulated by flavored food [74]. Treatment with zinc can be a possible option for improving taste in selected populations, but this has not been tested in patients with HF [112].

Based on the literature, it was hypothesized that demographic and psychosocial determinants could be of importance for appetite. As expected, in accordance with previous studies [43, 52], higher age was associated with poorer appetite in patients with HF (II). It is known that appetite generally deteriorates with increased age [43]. The knowledge of these relationships in HF is essential because the prevalence of HF increase with higher age. Although there were relationships between age and appetite problems, low appetite occurred in all age groups. It is therefore important to recognize appetite problems despite age, although special attention should be paid to the most elderly patients.

One important finding was that symptoms of depression was associated with appetite (II). These relationships have been found in other contexts [23, 50, 52], but this is the first study on HF. Research has shown that cardiac patients have lower mental health compared to other populations and that symptoms of depression are more prominent in HF compared to other cardiac diseases [113]. Still, the mechanisms behind the relationships between symptoms of depression and appetite are not clearly understood. One possible explanation could be that symptoms of depression may lead to a loss of interest to complete tasks. Thus, buying and preparing tasty food may not be a high priority, which can result in food becoming monotonous and not so appetizing.

Sleep deprivation is a common problem in patients with HF and it is more prevalent compared to general populations [21]. Yet, the associations between sleep and appetite have previously not been investigated. This thesis shows that insomnia is associated with decreased appetite (II). This

finding is important because low appetite assessed with CNAQ showed an increased risk of weight loss [7]. No previous studies exist to compare with HF, but the findings are in contrast with a review study that investigated sleep problems in a sample of adults. That study showed that people with sleep disturbances consumed poor quality food and fewer meals per day, which increased the risk for developing obesity [56]. As sleep problems are associated with decreased appetite, health care professionals should focus on appetite in patients with sleep problems and preferably include sleep habits in the nursing assessment.

The findings in this thesis showed that patients with better cognitive function generally had better appetite (II). No previous studies in HF have investigated the relationships between cognitive function and appetite. Studies in other populations with cognitive function as outcome variable have shown that decreased appetite is associated with poorer neurological function such as episodic memory, psychomotor-executive functions and verbal fluency [64]. In another nutrition study, it was shown that cognitive decline associated with impaired nutrition status [63]. Older peoples and the frailest have the most problems with appetite and these group of patients have also more cognitive problems. Cognitive function may contribute to declining nutrition status [62, 63]. As cognitive impairment is a common problem in patients with HF [57-59], these findings are of importance for clinical practice and research.

As for physical activity, the findings showed a relationship between physical activity and appetite (IV). Poor physical activity and poor appetite are both clinical issues, particularly in patients with severe HF. This study supported the assumption that also patients with mild HF display similar problems with physical activity and appetite. Another important finding was that physical activity predicted appetite at the 18-month follow-up. These results are in line with recent studies in older people, indicating that

physical activity and appetite seem to correlate [68]. However, it is difficult to determine which of the factors is the most important outcome. There are no similar studies, except one by Landi and colleagues. They investigated the opposite relationship, i.e., that appetite might affect physical activity [68]. The study was conducted in a frail population and not HF. Even though this thesis has appetite as outcome variable, these two studies strengthen each other as both show relationships between physical activity and appetite. Together, these findings show that physical activity should be considered in order to maintain or improve appetite in HF.

Physical activity in HF is important for improving health outcomes [9, 10, 114, 115]. This thesis showed similar results to what has been observed in other studies, i.e., that a large proportion of patients with HF have low physical activity levels [65, 116] that are comparable to a sedentary lifestyle in adults [117]. The patients in this thesis had lower physical activity levels regarding energy expenditure in kcal, number of steps and Mets daily average index compared to other studies [65]. One possible explanation could be that physical activity in this thesis was analyzed for four days, the compared study measured physical activity during 48 hours [65]. Short time in measuring physical activity might not completely reflect patient's habitual physical activity levels. Higher age and disease severity has been reported as contributing factors for low physical activity in patients with HF [65, 116] which support the current findings. In contrast, patients in the thesis performed similar six minutes' walk test as the sample in the HF-ACTION study, regardless of large age differences [118]. These findings illustrate that physical activity in HF is generally low and that age might have a negative influence on physical activity.

Changes in physical activity and appetite over time

Surprisingly, even though HF is a progressive disease, the results of this thesis did not show that appetite or physical activity changed significantly

over the study period of 18-month (IV). One explanation could be that the most severely ill patients had dropped out at the 18-month follow-up. There was a small trend of appetite and physical activity declining over time, but there were no significant changes. These findings indicate that appetite and physical activity are mostly stable over time, as long as the HF is stable. Prospective studies over a longer time period are needed to gain a more comprehensive understanding of the changes over time. Furthermore, aspects of nutrition status should be acknowledged in future studies.

Appetite, health and depressive moderation

This thesis found that better appetite associated with better health status (III). There were no available studies with which to compare findings in HF, but in other samples research has found different results. A large dataset from the Nutritional Day in Hospital survey showed that appetite predicted worse health status in hospitalized patients with chronic diseases [119] while other studies could not prove associations between appetite and health status in patients with chronic diseases [120]. There are several possible explanations for these disparities, for example, different study samples and methods for assessing appetite and health status. The findings in a study by Lainscak et al. [119] were based on a sample of general populations admitted to hospital. The assessments of appetite were based on questionnaires and health status was assessed with Likert-type scales. The study by Walke et al [120] was based on a sample of outpatients diagnosed with advanced COPD, HF and cancer, who required assistance in their daily lives. In the study, appetite was assessed with the VAS scale and health status was measured on a five-point response scale. Another possible explanation for the differences could be that the relationship is affected by symptoms of depression, a factor that none of the studies has taken into account [119, 120]. In this thesis, the associations between appetite and health status were affected by symptoms of depression. There is a relationship between these variables in patients who do not experience

symptoms of depression, while a relationship does not exist between these variables in patients who experience symptoms of depression. In other words, good appetite is important for having a good health status, but this was only evident in patients without symptoms of depression. These findings were evident after adjustments for age, gender and NYHA class (III). In light of previous research showing that depression and decreased appetite are important for health outcome [13, 121-123], health care professionals should pay extra attention to both symptoms of depression and appetite in order to identify patients at risk of developing impaired health status. So far, no prior studies have investigated symptoms of depression as moderator of the relationship between appetite and health status in HF populations. Therefore, additional studies are needed in order to confirm the current results.

Methodological considerations

This section includes a discussion about internal validity, external validity and statistical conclusion validity. This can help in understanding the results and judging the usefulness of the results in practice and their applicability in the care of patients with HF.

Internal validity

Internal validity can be referred to as the degree to which the investigator draws conclusions about what factors can affect validity [124]. In order to capture a broad understanding of the phenomenon appetite, the thesis was based on different study designs; psychometric evaluation (I), observational cross-sectional (II-IV) and observational prospective design with an 18-month follow-up (IV). A cross-sectional design was appropriate in study II in order to investigate the prevalence of decreased appetite [124]. In study II-III, important relationships were found, but as no conclusions about causal relationships can be drawn with a cross-sectional design the relationships may be reversed. In study IV, a longitudinal design

was used, which strengthens a possible causal relationship. A relationship were found between physical activity and appetite at baseline and at the 18-month follow-up.

It is a strength that patients from three hospitals were included, as care routines and organizations can affect the care. However, multicenter studies may increase the risk that measures differ between the study centers. For example, the weight scale was not calibrated between the centers. In addition, the six minutes' walk test might be assessed differently due to how patients were instructed to perform the test. To handle such potential problems, a study protocol was established. Education days and regular collaborating meetings were held to ensure uniformity between sites. With regard to the weight scale, these data were collected for descriptive purposes and were therefore not considered to be a problem for the outcomes. Moreover, multicenter studies require a large number of personnel and research resources. This thesis required three times more resources than if the study had been performed at a single center. Financial resources therefore need to be accounted for when designing clinical research.

It is essential to choose instruments that are validated for the intended group that will be studied. All instruments were validated, except the NRS scale for self-reported physical activity. However, only PHQ-9 for symptoms of depression and EQ-5D-3L for health status have been validated for use in cardiac patients. It is not always possible to use validated instruments for a particular patient group, and therefore, a decision needs to be made whether other instruments can be used. In this thesis, the instruments that were used were validated in elderly populations and in cardiac populations, which was considered acceptable. Furthermore, as appetite was central in this thesis, CNAQ was validated. The instrument was initially developed for a US elderly population.

Therefore, the CNAQ was translated into Swedish with guidance by the WHO criteria for translating and adapting instruments [78]. A limitation in this process was that the final Swedish items were not pre-validated from a patient perspective. Regarding content validity, it would have been valuable to conduct cognitive interviews with patients with HF to evaluate relevance, clarity, understanding, and sensitivity of the translated version of the CNAQ [125].

The CNAQ and SNAQ showed acceptable psychometrics. However, the validation study (I) did not include aspects of criterion validity, referring to the degree the instrument correlates with an external criterion. For example, the predictive validity was not explored, which limits the possibility to make predictions for a future outcome, for example weight loss [126]. Concurrent validity was not analyzed either, i.e., comparing the instrument's validity to an existing validated appetite scale. This could be seen as a limitation for the internal validity. However, there are no golden standard methods to assess appetite, which made it difficult to evaluate concurrent validity. Moreover, the instrument's validity was supported by the construct validity i.e., the instrument could distinguish groups of patients between low and high appetite such as symptoms of depression.

The self-reported questionnaire used in this thesis (I-IV) was completed by the patients in their homes. This approach might be a threat to the internal validity as patients could have discussed questionnaires and items with relatives or significant others. However, the risk for this was considered low as only a few patients had severe HF symptoms.

External validity

External validity refers to the investigators' conclusions about how the results can be applied to populations and events outside the study [124]. Generalization to a broader population than the inclusion criteria of the

sample in the study represents a threat to validity. The data collection was based on a sample of patients with stable HF in outpatient HF clinics. A total of 130 patients declined to participate and a study dropout analysis showed that the non-participants were older than the participants. Mean age was 71 years, which was slightly lower compared to other Swedish HF studies [36]. This might be considered a selection bias. However, the mean age was similar to other large international studies [11]. It was also shown that patients with higher NYHA class at baseline had dropped out at the 18-month follow-up. Appetite problems in this thesis are reflected by patients with stable, mild to moderate HF. As the most severely ill patients and the oldest patients were not included and/or lost in the follow-up assessment, it is likely that appetite problems are greater in the HF population than showed in this thesis. For this reason, one need to be careful about generalizing the findings to the oldest and those with severe HF.

Statistical conclusion validity

Statistical validity refers to the investigators' conclusions about the data analysis [127]. This thesis was based on an adequate sample size, which is important for statistical conclusion validity. Too small sample size increases the risk for type II errors. These appear when a relationship is missed when it actually exists, beta (β), which can further result in misleading conclusions of the study results [124]. In order to assure adequate sample size, power analyses were conducted for each study, except for study I. The analyses showed that the sample size was adequate for performing a regression analysis (II-IV), which strengthens the statistical conclusion validity. Regarding study I, previous studies has shown that 150-200 observations is large enough for medium sized (10-15 items) CFA models using WLSMW as estimation method [128]. As the CFA model of CNAQ included only eight indicator variables (i.e., items) and one latent variable, the sample size was probably sufficient large.

Most of the instruments that were used lack guidance to what is meaningful clinically changes or difference. To meet these, it is possible to calculate a type of effect size measure. In this thesis, R square (R^2) was used to interpret the effect size in the regression analyses (II-IV), which can be interpreted as 0.02 small, 0.13 medium, and 0.26 large effect. However, it had probably been more appropriate to use Cohens f^2 ($R^2/(1-R^2)$) interpreted as 0.02=small, 0.15=medium, 0.35=large effect [76]. There was no need to calculate any effect size regarding differences between the baseline data and the follow-up data in study IV, since there were no significant differences in appetite and physical activity.

It is recommended that statistical analysis methods correspond with the distribution of data and level of data. For example, parametric tests are recommended for normally distributed data and non-parametric tests are recommended for non-normally distributed data [103]. The statistical analysis in study I was based on ordinal data. In study II-IV, there were no appropriate non-parametric alternatives to linear regression. Possible alternatives would have been binary, nominal or ordinal regression models. However, all these models require the outcome variable to be categorized. In addition, the most appropriate logistic regression model for the present data, i.e., ordinal regression, can only handle small numbers of response categories in the outcome variable. For this reason, linear regression analyses were conducted in study II-IV.

Clinical implications

This thesis shows that appetite need attention clinically as 38% of the patients had appetite problems, despite that the majority had mild to moderate HF symptoms i.e., NYHA class II. The findings have important implications for the care of patients with HF. Appetite can be assessed with a validated instrument i.e., CNAQ and the results of the assessments can be used as a basis for communicating appetite with patients and their family members. Moreover, appetite can be assessed over time and decreased appetite can be recognized at an early stage, possibly before patients develop poor nutrition status. However, more studies are needed regarding the instrument's predictive value. Appetite is a common problem and assessments of appetite should preferably be incorporated as routine in nutritional care. This provides new knowledge and clinical experiences about appetite problems that can be used as a source for developing clinical routines in the care of patients with decreased appetite. Furthermore, several factors associated with decreased appetite imply that health care professionals should be particularly attentive to decreased appetite in patients who are older, as well as patients with symptoms of depression, sleeping problems, cognitive decline, low physical activity and patients with suboptimal medical HF treatment. In addition, as it was shown that higher levels of appetite are associated with better health status in patients without symptoms of depression, health care professionals should pay extra attention to appetite in patients with depressive symptoms.

Future research

This research project has resulted in new research questions that can be of importance for the care of patients with HF. The results guide future research to:

- Evaluate CNAQ's predictive value, i.e., if the dichotomized CNAQ score can predict weight loss also in HF.
- Explore the causal relationship between appetite and patient health outcomes.
- Describe patients' experiences of decreased appetite and health care professionals' experiences of caring for patients with decreased appetite.
- Explore the relationship between decreased appetite, salt and fluid restrictions.
- Investigate associations between self-reported appetite and biochemical appetite markers.

CONCLUSIONS

In order to improve the understanding of appetite in HF, the overall aim with this thesis was to investigate appetite in patients with heart failure, focusing on assessment, prevalence and related factors. The CNAQ has good measuring properties in HF but the instrument's predictive validity needs to be further examined in order to be used to identify patients with risk of developing malnutrition. The occurrence of appetite problems in HF is high, even in patients with stable HF, which indicates that these are important clinical problems that need to be taken seriously. Factors including older age, symptoms of depression, sleep problems, impaired cognitive function, impaired physical activity and patients with suboptimal medical treatment are associated with appetite in patients with HF and should therefore be recognized in the care of patients with HF. The fact that some of these factors had limited explanatory values and that appetite problems are common in HF appetite should be recognized in all patients with HF. Loss of appetite needs attention as it is likely to lead to worsened nutrition, but also because appetite is associated with health status. Finally, interventions that aim to improve appetite and thereby strengthen the patient's health status must take depression into account as the relationship between appetite and health status could not be detected in patients with symptoms of depression.

SVENSK SAMMANFATTNING

Att äta med god aptit är en naturlig del av livet men för patienter med hjärtsvikt är god aptit inte en självklarhet. När aptiten sviktar ökar risken för ett bristande näringsintag som i sin tur kan leda till undernäring med ökad sjuklighet, försämrad livskvalitet och tidig död. Forskning visar att nedsatt aptit vid hjärtsvikt troligen beror på onormala hormonella och inflammatoriska processer. Forskning har än så länge inte lett fram någon behandling för nedsatt aptit vid hjärtsvikt. Nutritionsråd vid hjärtsvikt handlar främst om att ge råd att begränsa vätske och saltintag medan patientens aptit inte särskilt uppmärksammas. En möjlig förklaring kan vara att det saknas kunskap kring hur aptit vid hjärtsvikt kan mätas. Det saknas kunskap kring hur förekommande problemet är och möjliga faktorer som kan vara relaterade till nedsatt aptit och även omvänt, hur nedsatt aptit påverkar patientens hälsa.

Syftet med avhandlingen var att undersöka aptit hos patienter med hjärtsvikt. Fyra studier ingick i avhandlingen där den första studien utvärderade ett aptitfrågeformulär för att eventuellt kunna användas som instrument för att mäta aptit. I andra och fjärde studien undersöktes hur vanligt det är med nedsatt aptit och vilka faktorer som skulle kunna ha betydelse för nedsatt aptit. I tredje studien undersöktes relationen mellan aptit och hälsa. Patienter ≥ 18 år med diagnos hjärtsvikt, med symtom på hjärtsvikt som följdes upp på hjärtsviktsmottagning tillfrågades att delta i studien. Vid första mätningen deltog 186 patienter varav 116 patienter från första mätningen deltog vid 18-månaders uppföljning. Patienterna fick besvara frågor om ålder, kön, boende, aptit, symptom på depression, hälsostatus, sömn, och fysisk aktivitet. Fysisk aktivitet registrerades också med en aktigraf som patienterna bar på överarmen under 7 dagar. Från patientens journal inhämtades information om hjärtsvikt, hälsohistoria

och läkemedelsbehandling. Även minnesfunktion, grad av hjärtsvikts symtom, funktionskapacitet och kroppssammansättning mättes. All data samlades i en databas och analyserades med hjälp av olika statistiska metoder utifrån avhandlingens syfte.

Majoriteten av patienterna hade milda till medelsvåra hjärtsviktssymtom. Medelålder var 71 år. Avhandlingen visar att aptitfrågeformuläret kan användas för att mäta aptit vid hjärtsvikt. Det framkom vidare att nedsatt aptit är ett vanligt problem, 38 % upplevde nedsatt aptit. Flera faktorer var kopplade till nedsatt aptit. Äldre patienter och patienter med symtom på depression, nedsatt sömn, nedsatt minnesförmåga, låg fysisk aktivitet och ej uppnådd rekommenderad dos av hjärtsvikts-medicinering var faktorer som relaterade till nedsatt aptit. Varken fysisk aktivitet, funktionskapacitet eller aptit förändrades över de 18 månader som patienterna följdes. Avhandlingen visar också att nedsatt aptit var kopplat till patientens hälsostatus med nedsatt rörlighet, mer smärta/obehag och mer ångest/depression. Patienter utan symtom på depression som skattade hög nivå av aptit hade generellt bättre hälsa.

Avhandlingen genererar ny viktig kunskap inom vård av patienter med hjärtsvikt. Vårdpersonal kan nu rutinmässigt mäta aptit vilket leder till att nutritionen uppmärksammas och åtgärder kan sättas in tidigt för att om möjligt förebygga och fördröja utveckling av undernäring. Vårdpersonal bör rikta särskild uppmärksamhet på aptit hos patienter som är äldre och patienter som har symtom på depression, nedsatt sömn, nedsatt minnesfunktion, suboptimal hjärtsviktsmedicinering och patienter som har låg fysisk aktivitet. Särskild uppmärksamhet bör riktas mot patienter som har symptom på depression eftersom denna faktor har en negativ inverkan på både aptit och hälsa

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APPENDIX. CNAQ and SNAQ

1 My appetite is

- ☐ very poor
- ☐ poor
- ☐ average
- ☐ good
- ☐ very good

2 When I eat

- ☐ I feel full after eating only a few mouthfuls
- ☐ I feel full after eating about a third of a meal
- ☐ I feel full after eating over half a meal
- ☐ I feel full after eating most of the meal
- ☐ I hardly ever feel full

3 I feel hungry

- ☐ rarely
- ☐ occasionally
- ☐ some of the time
- ☐ most of the time
- ☐ all of the time

4 Food tastes

- ☐ very bad
- ☐ bad
- ☐ average
- ☐ good
- ☐ very good

5 Compared to when I was younger, food tastes

- ☐ much worse
- ☐ worse
- ☐ just as good
- ☐ better
- ☐ much better

6 Normally I eat

- ☐ less than one meal a day
- ☐ one meal a day
- ☐ two meals a day
- ☐ three meals a day
- ☐ More than three meals a day

7 I feel sick or nauseated when I eat

- ☐ most times
- ☐ often
- ☐ sometimes
- ☐ rarely
- ☐ never

8 Most of the time my mood is

- ☐ very sad
- ☐ sad
- ☐ neither sad nor happy
- ☐ happy
- ☐ very happy

Council on Nutrition Appetite Questionnaire (CNAQ)

CNAQ = item 1-8. Items are scored from 1-5 where low score indicates low appetite.

A total score of CNAQ ≤ 28 indicates low appetite with risk of weight loss within six months.

Simplified Nutritional Appetite Questionnaire (SNAQ)

SNAQ = item 1, 2, 4, 6. Items are scored from 1-5 where low score indicates low appetite.

A total score of SNAQ ≤ 14 indicates low appetite with risk of weight loss within six months.

Papers

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