Cognitive function in elderly patients with chronic heart failure

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Thank you Roland and the rest of my family and friends for your support and understanding during this time

"It is not the brain that decides what you should think, it is the heart"

Emilia, age 14
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ABSTRACT

Introduction
Approximately 1-2% of the adult population in developed countries suffer from heart failure (HF), with the prevalence rising to more than 10% among patients 80 years of age or older. The HF syndrome is associated with elevated mortality and morbidity, and decreased quality of life. Cognitive dysfunction has been reported in patients suffering from a variety of cardiovascular disorders. However, few studies have systematically assessed cognitive performance in HF patients, its prevalence and other factors influencing cognition in HF patients. Further, it is of great interest to understand the relationship between self-care in HF and cognition. It may be important to screen for cognitive dysfunction as it may influence HF patients’ ability to perform self-care, e.g. make lifestyle changes, adhere to medical treatment and monitor, evaluate and treat symptoms of deterioration.

Aim
The overall aim of this thesis was to explore cognitive function in elderly patients with chronic heart failure with focus on prevalence, risk factors, sleep and self-care.

Design and method
This thesis is based on four quantitative studies. The data from study I and II were collected in a prospective longitudinal design, including Swedish same-sex twin pairs born in 1913 or earlier in Sweden. The study was conducted 1991-2002 and a total of 702 individuals aged 80 and older were included. Study III and IV had a cross-sectional design and included stable HF patients, median 72 years of age, living in the community in the south of Sweden. Data were collected between 2009 and 2012. Study III included a total of 137 patients and Study IV included 142 patients.

Results
Study I found that octogenarians with HF had significantly poorer spatial performance and episodic memory, and that the episodic memory declined more over time compared to a non-HF population of the same ages.
Study II showed that octogenarians with HF had a significantly higher prevalence of vascular dementia, 16% vs. 6%, and all types of dementia, 40% vs. 30%, than those not diagnosed with HF. Factors related to dementia in individuals with HF were depression, hypertension and increased levels of homocysteine. Diabetes was associated with an increased risk for vascular dementia.

In study III we found that HF patients with sleep disordered breathing (SDB) (apnoea-hypopnoea index >15) had significantly higher saturation time < 90%, more difficulties maintaining sleep and lower levels of daytime sleepiness compared to those in the non-SDB group. Cognitive function did not differ between the SDB and the non-SDB-group. Only insomnia was associated with a decreased global cognitive function measured with the Mini Mental State Examination instrument.

Finally, in study IV, the relationship between self-care and different dimensions of cognitive function was explored. Psycho- and visuomotor function (speed and attention) was the only dimension of cognitive function associated with self-care.

Conclusion
Octogenarians suffering from HF have a decreased performance in spatial and episodic memory and they also have a higher risk for developing dementia. Cognitive dysfunction as well as higher prevalence of dementia can contribute to decreased adherence to prescribed therapy and self-care management, and lead to other socio-behavioural problems.

Self-care was found to be associated with psychomotor speed. This may influence sustained attention negatively and the ability to carry out more than one task at the same time. This may lead to decreased attention for receiving and understanding information on self-care.

Keywords: chronic heart failure, cognitive dysfunction, dementia, elderly, oldest-old, prevalence, risk factors, self-care, sleep.
LIST OF PAPERS

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


### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ACE</td>
<td>Angiotensin-converting enzyme</td>
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<td>AHI</td>
<td>Apnoea-Hypopnea Index</td>
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<tr>
<td>ARB</td>
<td>Angiotensin receptor blocker</td>
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<td>BMI</td>
<td>Body Mass Index</td>
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<td>BNP</td>
<td>B-type Natriuretic Peptide</td>
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<td>CHF</td>
<td>Congestive Heart Failure</td>
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<tr>
<td>CVD</td>
<td>Cardiovascular disease</td>
</tr>
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<td>DMS</td>
<td>Difficult to Maintain Sleep</td>
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<td>EDS</td>
<td>Excessive Daytime Sleepiness</td>
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<tr>
<td>EHFScB-9</td>
<td>The European Heart Failure Self-Care Behaviour Scale</td>
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<td>ESS</td>
<td>Epworth Sleepiness Scale</td>
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<td>HF</td>
<td>Heart Failure</td>
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<tr>
<td>LVEF</td>
<td>Left Ventricular Ejection Fraction</td>
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<td>MISS</td>
<td>Minimal Insomnia Symptom Scale</td>
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<tr>
<td>MMSE</td>
<td>Mini-Mental State Examination</td>
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<td>MOCA</td>
<td>The Montreal Cognitive Assessment</td>
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<td>NYHA</td>
<td>New York Heart Association classification</td>
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<td>SDB</td>
<td>Sleep Disordered Breathing</td>
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INTRODUCTION

Approximately 1-2% of the adult population in developed countries suffer from heart failure (HF). The condition increases with age to more than 10% in individuals 80 years of age and older (Roger et al. 2012). Heart failure is a chronic condition where the heart is unable to provide the different organs with adequate circulation of blood due to abnormality in the heart and changes in the hemodynamic, kidney-, nerve and hormone system (McMurray et al. 2012). Heart failure is associated with poor prognosis and treatment is complex and contains multi-drug regimens and lifestyle changes (McMurray et al. 2012). Adherence to treatment is essential for clinical outcomes such as survival and health-related quality of life (van der Wal et al. 2005). Factors such as cognitive dysfunction and comorbidities can affect adherence to treatment (Moser et al. 2012, Pressler et al. 2010a).

Cognitive functioning is essential for independence, health-related quality of life and survival, especially in late life. A better understanding of the factors that contribute to maintaining cognitive functioning in late life is important for the patients, but also for the society in general. It is important that healthcare staff is aware of the risk factors associated with cognitive dysfunction and dementia in elderly HF patients in order to optimise patient education and support to improve self-care.

Risk factors of interest in patients with HF in relation to cognitive function is therefore important to investigate. Sleep disordered breathing (SDB) is a common risk factor in HF patients and it is associated with insomnia and/or excessive daytime sleepiness, which are known to affect cognitive function (Heckman et al. 2007, Zimmerman & Aloia 2012).

From a nursing perspective, a combination of subjective and objective assessment of cognition, dementia and sleep deprivation is important for understanding the patients’ needs (Cameron 2010, Cameron et al. 2012, Riegel & Weaver 2009). Nurses and other caregivers usually observe and evaluate the patient’s need of information and self-care activities (Moser et al. 2012). Therefore, it is important to explore cognitive function, with regard to prevalence, risk factors and associations between cognition and self-care performance among HF patients, in order to increase knowledge among nurses and other healthcare professionals.
BACKGROUND

Heart failure

Definition, etiology and epidemiology

Heart failure is a complex syndrome and the most common reason for hospitalisation and rehospitalisation among older adults (Lloyd-Jones et al. 2010). There are many causes of HF which vary in different parts of the world. The main causes for developing HF are ischemic heart disease, hypertension, diabetes and coronary artery disease. There are several pathophysiological pathways that are the main causes for developing HF. However, there seems to be a point where a structural remodeling of the myocardium starts, which leads to a pump dysfunction or HF (Dickstein et al. 2008, McMurray et al. 2012).

Heart failure is progressive and fatal, but it can be stabilised spontaneously or after therapy. There is a difference between acute and chronic HF. Acute HF is characterised by a rapid onset of symptoms and insufficient cardiac function, in contrast to chronic HF which seldom presents with acute exacerbations (Nieminen et al. 2005, Swedberg et al. 2005).

The prevalence of HF is between 1 and 2% and rises sharply at the age of 75 to more than 10% by the age of 80 and older. In the elderly, prevalence of HF is equal between the sexes. In younger age groups, HF is more common in males because coronary heart disease occurs earlier in that group (McMurray et al. 2012). In Sweden, the estimated prevalence of HF is 2.2%, incidence 3.8/1000 patient/years. There has been a decrease in incidence and mortality from 2006 to 2010 in both men and women, with no change in prevalence over time (Zarrinkoub et al. 2013).

Symptoms and disease severity

The most common symptoms of HF are shortness of breath, fatigue, exercise intolerance and peripheral oedema. To state the degree of functional status and symptoms severity in HF, the New York Heart Association functional
classification (NYHA) has been developed by (The Criteria Committee of the New York Heart Association 1973) (Table 1).

<table>
<thead>
<tr>
<th>NYHA class</th>
<th>Description</th>
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<tr>
<td>I</td>
<td>No limitations, ordinary physical exercise does not cause undue fatigue, dyspnea or palpitations.</td>
</tr>
<tr>
<td>II</td>
<td>Slight limitation of physical activity, comfortable at rest but ordinary activities result in fatigue, dyspnea or palpitations.</td>
</tr>
<tr>
<td>III</td>
<td>Marked limitation of physical activity, comfortable at rest but less than ordinary activities result in fatigue, dyspnea or palpitations.</td>
</tr>
<tr>
<td>IV</td>
<td>Unable to carry out any physical activity without discomfort, symptoms of heart failure are present even at rest with increased discomfort with any physical activity.</td>
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There is a weak relationship between the NYHA classification and objective tests of cardiac dysfunction. Using echocardiogram, provide information on chamber volumes, ventricular systolic and diastolic function, wall thickness, and valve function (Borlaug et al. 2011, McMurray et al. 2012). Other tools used as markers of disease severity such as increased plasma concentrations of brain natriuretic peptides, B-type natriuretic peptide (BNP) and its precursor N-terminal fragment (NT-proBNP), have been found to reflect cardiac function. These have also been used as tools for diagnosing HF (Alehagen et al. 2003, Weber & Hamm 2006). No definitive cut-off value has however been recognised for BNP (Weber & Hamm 2006), but a value lower than 100 pg/ml is considered as normal (Januzzi 2012).

**Prognosis**

Heart failure is a leading cause of hospitalisation in the elderly and prognosis is poor with half of the patients dying within a few years after diagnosis.
Background

Recent data however, suggest a decrease in mortality (Zarrinkoub et al. 2013). Morbidity is higher in elderly than in younger HF patients (Heart Failure Society of America 2006). A better understanding of factors related to mortality and morbidity may help to identify patients who are in need of more intensive monitoring therapy and additional interventions (Pocock et al. 2006).

Treatment

The treatment goals for patients with HF are to relieve symptoms and signs, prevent hospital admission, and improve survival. This is often accompanied by reverse left ventricular remodelling and reduction in circulation natriuretic peptide concentrations (Masson et al. 2008). Reduction in mortality and hospital admission rate reflects the ability of effective treatments to slow down worsening HF. Pharmacological therapy is based on the use of angiotensin-converting enzyme inhibitors, and/or angiotensin II receptor blockers, beta-blockers, mineralcorticoid receptor antagonist and diuretics (McMurray et al. 2012).

Sometimes, surgical therapy is warranted in cases where HF is caused by a surgically correctable condition, such as valve or coronary artery disease. Furthermore, surgery with left ventricular devices or heart transplantation can be done in severe cases of cardiomyopathy (Nicolini & Gherli 2009). Implantable Cardioverter defibrillator (ICD) or cardiac resynchronisation therapy (CRT) are other treatment options. CRT implantation should be considered only after a sufficient period of medical therapy optimisation of 3 months, and if patients remain symptomatic. ICD implantation is indicated in patients at risk or already presenting with life-treating arrhythmias. Patients should be informed about related complications (inappropriate shocks) and deactivation opportunities at end-of-life before implantation (Stewart et al. 2010, McMurray et al. 2012).

Treatment also includes non-pharmacological treatment, based on education and counselling to promote patients’ self-care behaviour in order to improve or maintain health. Important topics for education are HF pathophysiology, monitoring of symptoms, daily weight, pharmacological treatment, prognosis, advice about lifestyle changes such as dietary changes, fluid restrictions and exercise recommendations (Sears et al. 2013, Riegel et al. 2011, Moser et al. 2012). Healthcare providers need to emphasize treatment adherence among HF patients. Adherence to medication in HF patients is an acknowledged problem. The World Health Organisation report that up to 50% of individuals
with chronic diseases do not adhere to their medication and when it comes to exercise and diet advice the numbers are even lower (van der Wal et al. 2010, van der Wal et al. 2006). Factors that influence adherence are related to the disease effects of the treatment, personality of the patient, social and economic context, the patient-physician communication, and the healthcare system (Krueger et al. 2005, Vermeire et al. 2001, World Health Organization 2003). Nonadherence can be regarded as unplanned relating to issues of cognition (e.g. forgetfulness), ability to read and write and quickness of using the hands, or intentional where beliefs about a medicine (side effects) or costs of the medicine result in not taken the medication (World Health Organization 2003, Vermeire et al. 2001).

Cognitive function

Cognitive abilities

Definition of a decline in a cognitive function is called cognitive dysfunction or impairment. It can also be mentioned as abnormality or disability. In this thesis we have chosen cognitive dysfunction as the term to use for a decline in cognitive function.

Cognitive ability refers to the internal mental processes, such as memory and thinking. It is of importance to identify, measure, and distinguish between abilities that underlie the complex nature of thinking and the processing of information. Cognitive function was originally attributed to a single function, intelligence (Lezak et al. 2004), but neuropsychological studies have not found a general cognitive or intellectual function (Duncan et al. 2000). Cognitive abilities is the term used when referring to information reception, processing, expression and executive functions (Ardila 1999). Memory, verbal abilities, spatial abilities, and processing speed are some other abilities that are considered to be chore aspects off cognition (Horn & Cattell 1967). There are four major classes of cognitive functions that have their analogues in the computer operations of input, storage, processing (sorting, combining and relating data in various ways), and output. Perception involve the abilities to select, acquire, classify, and integrate information (Ardila 1999). Memory and learning refer to information storage and retrieval. Thinking concerns the mental organisation and reorganisation of information and
expressive and executive functions are the means through which information is communicated or acted upon (Lezak et al. 2004). The same patterns can be found among younger and healthy elderly individuals within the taxonomy of memory (Figure 1).

Memory is divided in short-term (blue color in Figure 1) and long-term memory (dark green color in Figure 1). Short-term memory includes verbal input/output with articulatory and phonological rehearsal. It also includes the visuospatial "sketch pad", which is the working memory for visual information on how a person recalls visual stimulus, for example recognising surroundings and faces (Benton & Hécaen 1970).

Human short-term memory also includes the episodic buffer and a central executive that allocates attentional effort. The episodic buffer is not permanent but link visual, spatial and verbal information across different sensory modalities (Baddeley 1974). The episodic buffer links the short term to the long-term memory (episodic and semantic). An example of an episodic buffer is when you remember a story or a movie scene (Babcock & Salthouse 1990).

Attentional cognitive effort concerns recognition and execution and selection of output action. In many contemporary theories of short-term memory, attention is regulated by one or several executive systems. Typically, central executive is called upon when task requirements exceed the capacities of the simpler and more automatic buffer systems.

Procedural memory (lighter green color in Figure 1) is the implicit, unconscious memory which includes priming with the automatic response and repetition to later stimulus (Squire & Zola-Morgan 1991). Procedural memories include learning skills which are dependent on different perceptual experiences. Priming is an automatic response and repetition to later stimulus. Classic conditioning is when individuals evidence psychological reactions to an event, for instance in connection with an accident and experience fear and accidental happenings.

Declarative memory is the conscious memory involving recalled facts and knowledge (Squire & Zola-Morgan 1991). Episodic memory is the memory of autobiographical events (times, places, associated emotions, personal, contextual knowledge) (Babcock & Salthouse 1990).

Semantic memory is the factual information and general knowledge about the world, for example what we learnt at school (Tulving 1972). To measure short-term and long-term memory, a brief neuropsychological test battery,
Background

competence to perform them and specialist education are needed (Diller 2000, Sohlberg 2001).
Figure 1. The taxonomy of the memory describing cognitive function and the cognitive tests used in this thesis to measure different aspects of cognitive function.
Background

Cognitive assessment

There are several different types of cognitive tests evaluating a person’s global ability to perceive relationships and solve problems (Stanek et al. 2009). Assessments in the cognitive domains include language, attention, concentration, visuospatial perception and constructional abilities, frontal systems/executive functions, verbal/non-verbal learning and memory. Sensory and motor functions, as well as general intellectual functioning are also routinely assessed (Lezak et al. 2004). Qualitative observations and quantitative scores are evaluated together once all data from neuropsychological examinations, patients’ history, background, and present situation have been collected (Diller 2000, Sohlberg 2001). A neuropsychological examination in patients with HF can answer questions concerning the patient’s ability to perform self-care, including adherence to the treatment regimen (van der Wal et al. 2006, van der Wal et al. 2010).

Comorbidity affecting cognitive function and HF

There is a high degree of comorbidity (defined as the presence of one or more related disorders or diseases) and multiple morbidity (defined as two or more separate long-term conditions)(Fortin et al. 2007) among patients with HF. The degree of comorbidity varies slightly among HF patients with preserved or reduced left ventricular ejection fraction (Triposkiadis & Skoularigis 2012). The occurrence of comorbidities and multi-morbidity may influence both HF and cognitive function (McMurray et al. 2012, Pressler et al. 2010a).

Depression is defined by the presence of affective, cognitive, psychomotor and somatic symptoms (Veiel 1997, American Psychiatric Association 2000). Depression has an impact on both cognitive function (Garcia et al. 2011) and normal sleep (Kociuba et al. 2010, Almeida et al. 2005, Johansson et al. 2012), and affects self-care performance in HF patients (Johansson et al. 2006). The prevalence of depression is at least 50% in HF patients (Gottlieb et al. 2004). Recent studies have implied that Major depression (MD) could be a risk factor for developing Alzheimer’s disease. Major depression is a severe mental disorder characterised by alterations in mood and cognition (Sierksma et al. 2009). Depression and vascular disease share common pathophysiological
processes with microvascular lesions in the brain, the same as in cognitive dysfunction (Camus et al. 2004).

Older adults with diabetes are at an increased risk of cognitive dysfunction with regard to verbal learning, memory problems, working memory and psychomotor function (Knopman et al. 2001). Diabetes is a risk factor for the development of cardiovascular disease and HF (Fortin et al. 2007, Lu et al. 2009), and is associated with an increased risk of multi system complications associated with substantial morbidity and adverse outcomes. Some of the problems (cognitive dysfunction, mobility impairment) may significantly interfere with disease management (Inouye et al. 2007, Lu et al. 2009).

Hypertension has been associated with mild cognitive impairments and it can be a causal risk factor for HF, or it may co-exist with another primary etiology (Dickstein et al. 2008). Untreated hypertension is an important predictor of poor cognitive outcome in older adults. Onset of hypertension in late life is very common (attributable to arterial stiffness), and may have different implications for cognitive function compared to early onset (Swan et al. 1998). A recent study showed that cognitive dysfunction induced by impaired microcirculation is linked to large artery stiffness and microvascular damage (Triantafyllidi et al. 2009).

Dementia

Alzheimer’s disease is the most common type of dementia. There are great differences regarding symptoms among patients. Two patients do not present the same symptoms. However, in the end all functions are lost and all patients reach a similar stage of behaviour. More than two-thirds of all cases of dementia are attributed to this condition (Skoog 2001). Alzheimer’s disease is predicted to increase in patients with HF due to an increasingly aging population (Polidori et al. 2006), and 75% of the patients with Alzheimer’s disease have cognitive dysfunction and affect the ability of patients to perform self-care (Qiu et al. 2010, Vogels et al. 2007b).

Vascular disease and multi-infarct dementia are conditions where widespread cognitive dysfunction takes place as a result of repeated infarctions (Meyer 1997). Cardiovascular insufficiency in elderly individuals who have not suffered a major stroke or heart attack accounts for 28% of the variance in performance of conceptual abstraction and flexibility (Dywan 1992). Mild cognitive impairment has been discussed as a potential preclinical form of
dementia (Etgen et al. 2009) that increases with age and HF (Polidori et al. 2006).

**Sleep disorders and cognitive function**

Poor sleep is associated with reduced global cognitive function (Kociuba et al. 2010). The most common primary sleep disorders in elderly individuals are sleep disordered breathing (SDB), insomnia and excessive daytime sleepiness (Cameron et al. 2012, Johansson et al. 2010, Johansson et al. 2009). The definition of SDB is an apnoea-hypopnoea index (AHI) >5 (Oldenburg et al. 2007), and has been recognised as a major problem among HF patients as it leads to disrupted sleep (Somers et al. 2008, Cormican & Williams 2005). Sleep disordered breathing occurs in >7 out of 10 HF patients in NYHA functional class ≥ II (Oldenburg et al. 2007). Patients with HF might suffer from different types of breathing disturbances (obstructive and central sleep apnoea). Obstructive sleep apnoea is found in up to 40% and central sleep apnoea is even more common (Duran et al. 2001).

Insomnia (i.e. difficulties initiating sleep, difficulties maintaining sleep and non-restorative sleep) is another prevalent type of sleep disturbance in older patients with HF (Johansson et al. 2009, Brostrom et al. 2004). Insomnia is often regarded as a symptom of various underlying disorders, such as SDB (Brostrom & Johansson 2005). Disrupted sleep leads to various daytime effects such as fatigue, listlessness, bad memory and ability to concentrate (Cacciatore et al. 1998, Vogels et al. 2007a). The definition of excessive daytime sleepiness is “sleepiness in a situation when an individual would be expected to be awake and alert” (Arand et al. 2005). Excessive daytime sleepiness is characterised by haunting sleepiness and often a general lack of energy, even after an adequate night’s sleep. It is not clear whether fatigue should be a part of excessive daytime sleepiness as fatigue can be described as weariness, weakness or loss of energy (Ohayon 2008).

Sleep loss and fragmentation affect cognitive functions such as memory encoding, consolidation, plasticity and reconsolidation (Kalia 2006). Furthermore, executive functions, including decision-making processes (Killgore et al. 2006), and attention and psychomotor speed are also affected by disturbed sleep (Durmer & Dinges 2005). A recent study in adults (mean age 62.8 years) with cardiovascular disease showed that poor sleep was observed in 94% of the patients and was independently associated with reduced cognitive function (Kociuba et al. 2010). Two other recent studies (Hellstrom et
Background

al. 2010, Yaffe et al. 2011) show that hypoxia caused by apnoeic events can be an indicator of cognitive dysfunction and dementia. Sleep problems may also be of importance for the development of early atherosclerosis and vascular dementia in patients with CHF (Yaffe et al. 2011).

Self-care in heart failure and its relation with cognitive function

Self-care is identified as one of the most important parts of successful HF treatment and education is found to improve patients’ abilities to care for themselves (Dickson et al. 2007, McMurray et al. 2012). The ability to learn and to keep and use information is a central point in a self-care program for HF patients (Strömberg 2005, Wolfe et al. 2006). Self-care is a decision-making process requiring the cognitive ability to learn, perceive, interpret and reason, and give response (Riegel et al. 2013). Healthcare professionals are advice to provide information about regular weight monitoring, sodium, fluid, alcohol intake, smoking, immunisation, activity and exercise, sexual activity, pregnancy, travelling, sleep disorders, depression and mood disorders, and even prognosis. It is important that the patient and the family understand the factors that influence prognosis (Dickstein et al. 2008, McMurray et al. 2012). Patients need adequate knowledge of their medical treatment, especially regarding effects, side effects, and how the medications should be taken and titrated. Patients and/or caregivers also need to recognise the symptoms and take appropriate action, such as increasing the prescribed diuretic dose and/or contact the healthcare team (Riegel et al. 2002, Dickson et al. 2007, McMurray et al. 2012). To increase adherence and ability to adapt, a structured and individually adjusted patient education is needed (Wolfe et al. 2006).

Self-care requires that patients make decisions about symptoms, but the cognitive deficits documented in 30% to 50% of the heart failure population may make daily decision-making challenging (Cameron 2010, Vogels et al. 2007b). It is important to screen for cognitive dysfunction as it has a large impact on the patient’s ability to learn and adapt to self-care management in HF and adhere to medical treatment (Stromberg et al. 2006).

Cognitive dysfunction results in problems with understanding and receiving information, remembering and acting when symptoms occur (Strömberg 2005, Wolfe et al. 2006). This puts high demands on nurses and other caregivers to be sensitive and to be able to teach self-care (Strömberg 2005). Structured patient education and follow-up have been shown to reduce mortality and morbidity
among chronic heart failure patients (McAlister et al. 2004, Stromberg et al. 2003). These types of follow-up and education in nurse-based heart failure clinics have been found to be especially beneficial for people with cognitive dysfunction (Karlsson et al. 2005). HF patients with cognitive dysfunction run a higher risk of not attending follow-up e.g. at a heart failure clinic (Ekman et al. 2001). In this area, nurses can perform many activities to assist the patients. Orem has classified these actions into five categories: (1) act or do for others, (2) guide or direct others, (3) support, either physically or psychologically, (4) provide an appropriate environment for care to be delivered and personal abilities to be developed, (5) to teach (Orem 1991). Orem has developed a grand theory of self-care. Riegel and colleagues have described a middle-range theory of self-care in chronic illness (Riegel et al. 2012). They emphasise that all healthcare professionals have a role in promoting self-care. The concepts in the middle-range theory are self-care maintenance, self-care monitoring and self-care management. Self-care maintenance is defined as behaviours to maintain physical and emotional stability. Self-care monitoring refers to the process of observing changes in signs and symptoms in oneself, whereas self-care management is defined as the response to signs and symptoms when they occur. Self-care management is a process of recognising changes in signs and symptoms, making decisions on self-care actions and evaluating the outcomes of an action. Riegel and colleagues describe that each element is unique and functions in a synchronic way to maintain health and manage illness, and that there is a variety of factors that influence individual patients’ in performing self-care actions (Riegel et al. 2012).

Self-care in HF has also been described as a naturalistic decision-making process, where patients use informal reasoning and previous experience to choose reasonable options, which is reflected in descriptions of naturalistic decision-making (Riegel et al. 2013). There are two schools for describing decision-making processes, normative and descriptive. Normative decision-making is an analytic process were patients search and make analysis of available information. Independent values are weighted between advantages and disadvantages before making a choice (Lipshitz 2001). Descriptive decision-making evolved in response to recognition, it is used to explain how people make decisions in the real world. Decision-makers have limited time and options, and mistakes are made when complex and dynamic situations are considered. The leading descriptive model is the naturalistic decision-making process. Naturalistic decision-making has primarily been used to explain how experts make work-related decisions (Bond & Cooper 2006), but the principles also apply to individuals making personal decisions (Riegel et al. 2012).
Background

2013). Naturalistic decision-making appears to be a good description of the real world process used by HF patients (Riegel et al. 2013).
RATIONALE FOR THE THESIS

Heart failure is a common diagnosis in western countries and the prognosis is poorer than most common form of cancer. Cognitive dysfunction is a prevalent and complicating condition in HF and can appear in different situations, for instance in connection with different comorbidities, aging or dementia. All these conditions can make patients vulnerable and in need of support to manage HF self-care in their daily life.

This thesis aimed to investigate how common cognitive dysfunction is in an elderly-elderly population, above 80 years of age and among middle-aged and elderly HF patients with less severe heart failure. Further, this thesis focuses on risk factors for cognitive dysfunction and dementia in patients with HF. By improving knowledge on this screening, prevention and interventions to improve cognition in HF can be developed.

Sleep problems including SDB, insomnia and excessive daytime sleepiness have also been studied in this thesis since sleep is known to influence both cognition and self-care in HF. Another co-morbidity that influences sleep, cognition and self-care is depression which is common in persons with HF. Depression has been found to affect normal sleep and cognitive function. Patients with HF are at an elevated risk for cognitive dysfunction that affect HF patients to adhere to self-care.

Adequate self-care behaviour is of great importance in patients suffering from HF and reflects the actions that a patient undertakes to maintain healthy functioning and wellbeing. Therefore, self-care behaviour is central in this thesis and in the final study we studied the relationship between cognitive function, sleep, depression and self-care.
AIMS OF THE THESIS

The overall aim of this thesis was to explore cognitive function in elderly individuals with chronic heart failure with focus on prevalence, risk factors, sleep and self-care.

Specific aims

Aim I
To examine the relationship between heart failure and specific cognitive abilities in octogenarians with regard to level and change over time.

Aim II
To compare the prevalence of dementia in individuals 80 years or older with CHF and those in the same age group without CHF, and to identify the factors related to dementia in individuals diagnosed with CHF.

Aim III
To compare sleep and wake patterns, insomnia, daytime sleepiness and cognitive function in community-dwelling CHF patients, with and without SDB, and to investigate the association between sleep-related factors and cognitive dysfunction.

Aim IV
To test the relationship between cognitive function and self-care in patients with heart failure after adjusting for the contribution of age, education, functional status, myocardial stress, sleep and depression. Further, the relationship between cognitive function and self-care was explored with symptoms of depression and sleep as moderators.
MATERIAL AND METHODS

Design and setting

This thesis comprises of four quantitative studies. Study I and II have a prospective longitudinal design. Data was collected in Sweden between 1991-2002 in a twin study called OCTO-Twin (Cederløf & Lorich 1978). The data collection took place in the participant’s home during 5 measurement occasions, called In-Person-Testing (IPT), with 2-year intervals between.

In study II, demographic and clinical characteristics were from the IPT 2 performed years 1993-1995, laboratory samples were collected those years. Study III and IV had a descriptive, cross-sectional design including participants from one university hospital and two county hospitals in southern Sweden. Demographic and clinical characteristics are shown in Table 2.
Table 2. Demographic and clinical characteristics in study I and II, III and IV.

<table>
<thead>
<tr>
<th></th>
<th>HF patients study I Baseline N=95</th>
<th>HF patients study II IPT 2 N=138</th>
<th>HF patients study III N=137</th>
<th>HF patients study IV N=142</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age a</strong> m±sd</td>
<td>84.34 ±4.05</td>
<td>86.56 ±3.69</td>
<td>72 (64-76) d</td>
<td>72 (65-79) d</td>
</tr>
<tr>
<td><strong>Female gender b</strong></td>
<td>64 (67)</td>
<td>88 (64)</td>
<td>44 (32)</td>
<td>45 (32)</td>
</tr>
<tr>
<td><strong>Years of education b</strong> m±sd</td>
<td>6.74 ±2.2</td>
<td>7.14 ±2.3</td>
<td>&gt;9years 56(41)</td>
<td>&gt;9years 58(41)</td>
</tr>
</tbody>
</table>

**Clinical variables**

<table>
<thead>
<tr>
<th></th>
<th>m±sd</th>
<th>m±sd</th>
<th>m±sd</th>
<th>m±sd</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BMI a</strong></td>
<td>24.02 ±4.22</td>
<td>24.45 ±4.07</td>
<td>28 (24-31) d</td>
<td>28 (25-32) d</td>
</tr>
<tr>
<td><strong>Waist circumference m±sd</strong></td>
<td>89.89 ±11.9</td>
<td>90.11 ±12.0</td>
<td>104 ±15.5</td>
<td>104 ±15.5</td>
</tr>
<tr>
<td><strong>BNP</strong></td>
<td>-</td>
<td>-</td>
<td>136 (60-263) d</td>
<td>140 (60-263) d</td>
</tr>
<tr>
<td><strong>Smoker b</strong></td>
<td>29 (30)</td>
<td>42 (30)</td>
<td>17 (12)</td>
<td>17 (12)</td>
</tr>
<tr>
<td><strong>Systolic recumbent blood pressure(mmHg) a</strong> m±sd</td>
<td>159.04</td>
<td>159.92 ±23.6</td>
<td>125 ±21.35</td>
<td>125 ±21.28</td>
</tr>
<tr>
<td><strong>Diastolic recumbent blood pressure(mmHg) a</strong> m±sd</td>
<td>80.86 ±12.0</td>
<td>83.85 ±13.9</td>
<td>74.08 ±11.95</td>
<td>73.88 ±12.09</td>
</tr>
<tr>
<td><strong>Arterial hypertension&gt;140/90 mmHg</strong></td>
<td>42 (31)</td>
<td>42 (30)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Creatinine (μmol/l) a</strong> m±sd</td>
<td>88.55</td>
<td>88.78 ±27.6</td>
<td>104 (81-130) d</td>
<td>103 (82-130) d</td>
</tr>
<tr>
<td><strong>Urea (mmol/l) a</strong></td>
<td>8.98 ±3.25</td>
<td>8.81 ±3.37</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Urate (μmol/l) a</strong></td>
<td>425.64 ±118</td>
<td>415.04 ±146</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Homocysteine (μmol/l) a</strong> m±sd</td>
<td>20.03 ±7.2</td>
<td>20.13 ±7.8</td>
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<td>-</td>
</tr>
</tbody>
</table>

**Comorbidities**

<table>
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<tr>
<th></th>
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<th>m±sd</th>
<th>m±sd</th>
<th>m±sd</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diabetes b</strong></td>
<td>23 (24)</td>
<td>23 (17)</td>
<td>24 (17)</td>
<td>24 (17)</td>
</tr>
<tr>
<td><strong>Obstructive lung diseases b</strong></td>
<td>15 (16)</td>
<td>18 (13)</td>
<td>5 (4)</td>
<td>5 (3.5)</td>
</tr>
<tr>
<td><strong>Angina Pectoris b</strong></td>
<td>33 (35)</td>
<td>39 (28)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Myocardial infarction b</strong></td>
<td>28 (29)</td>
<td>38 (27)</td>
<td>30 (22)</td>
<td>30 (21)</td>
</tr>
<tr>
<td><strong>Stroke b</strong></td>
<td>33 (35)</td>
<td>41 (30)</td>
<td>9 (7)</td>
<td>9 (6)</td>
</tr>
<tr>
<td><strong>Parkinson’s disease b</strong></td>
<td>7 (5)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Depression b</strong></td>
<td>12 (13)</td>
<td>17 (12)</td>
<td>53 (39)</td>
<td>57 (40)</td>
</tr>
</tbody>
</table>

**Medication**

<table>
<thead>
<tr>
<th></th>
<th>m±sd</th>
<th>m±sd</th>
<th>m±sd</th>
<th>m±sd</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diuretics b,c</strong></td>
<td>57 (60)</td>
<td>67 (48)</td>
<td>81 (59)</td>
<td>109 (77)</td>
</tr>
<tr>
<td><strong>Betablocker b,c</strong></td>
<td>14 (15)</td>
<td>13 (9)</td>
<td>100 (73)</td>
<td>132 (92)</td>
</tr>
<tr>
<td><strong>Calcium-antagonist b,c</strong></td>
<td>2 (2)</td>
<td>3 (2)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Digitalis</strong></td>
<td>-</td>
<td>-</td>
<td>9 (7)</td>
<td>15 (10)</td>
</tr>
<tr>
<td><strong>Angiotensin converting inhibitor b,c</strong></td>
<td>5 (5)</td>
<td>13 (9)</td>
<td>63 (46)</td>
<td>83 (58)</td>
</tr>
<tr>
<td><strong>Angiotensin II receptor blockers</strong></td>
<td>-</td>
<td>-</td>
<td>44 (32)</td>
<td>58 (41)</td>
</tr>
<tr>
<td><strong>Mineralcorticoid receptor antagonist</strong></td>
<td>-</td>
<td>-</td>
<td>35 (25)</td>
<td>47 (33)</td>
</tr>
</tbody>
</table>

Note: Frequency and percent n (%) unless otherwise stated. a= t-test independent sample, b= chi2 pearson, c= medication at time 2 (study I and II), d= median quartile (1-3)
Study participants

All subjects in study I and II originated from the OCTO- twin population designed to investigate bio-behavioural functioning among the oldest old (Cederlof & Lorich 1978). A total of 702 individuals aged 80 and older were included in the study, at baseline there was 95 HF patients (Figure 2). All same-sex twin pairs 80 years of age and older, with both members still alive during IPT 1 (1991-1993), were identified as potential participants. A letter describing the nature and purpose of the study was mailed to 1474 individual twins (737 pairs). They were then contacted by telephone and asked to participate. Of these, 376 individuals (188 pairs) were excluded because one or both members died before testing was scheduled. In addition, 396 individuals (198 pairs) were excluded because one or both members of the pair declined participation. A total of 702 individuals, 234 male and 458 female participated. Mean age was 83.6 (SD 3.2) and median age 82.5 years. No significant differences were found between monocytic and dizygotic twins (Nilsson et al. 2002).

Data from study III and IV were collected consecutively from community-dwelling patients in the south of Sweden between 2009-2012. Inclusion criteria were 18 years of age and HF based on the European Society of Cardiology guidelines (Dickstein et al. 2008). For study inclusion in study III and IV, see Figure 3.
Material and methods

Figure 3. Participants flow in study III-IV.

Data measurements

Assessment of cognition

In this thesis, a brief neuropsychological test battery of instruments measuring cognitive function was used in different cognitive areas. Different instruments were used in study I-IV, depending on research questions and different approaches. All instruments are commonly used in neuropsychological testing (Lezak et al. 2004). An overview of the tests is shown in Table 3.
Global cognitive function

In study II, III and IV, global cognitive function was measured with Mini-Mental State Examination (MMSE), this is a well-known cognitive screening test with 11 items. MMSE contains questions about different cognitive abilities such as orientation, attention and concentration, sequence, visual-spatial abilities, verbal learning and memory, reading aloud, understanding and verbal repetition. MMSE is validity tested and reliability is high (Folstein 1975). The maximum score is 30 (Folstein 1975). A score ≥ 28 indicates normal cognitive function, 25-27 indicates mild cognitive dysfunction and MMSE ≤ 24 is considered to indicate cognitive dysfunction with a high risk for dementia (Crum et al. 1993).

Psychomotor speed and Executive function

Attentional capacity effort concerns the recognition and execution of stimulus. Procedural memory is the implicit, unconscious memory which includes priming with the automatic response and repetition to later stimulus (Squire & Zola-Morgan 1991). Processing Speed (Study I and II) was measured by; 1. Symbol Digit Test, a modified version of the Wechsler Adult Intelligence scale. The test requires a verbal response in the appropriate digit that matches a printed symbol. The score is the sum of the correct numbers of symbol digits in two 45-second trials. 2. Perceptual Speed is a timed picture matching task (figural similarity). The participant is asked to detect one item among five alternatives identical to the target item presented (Wechsler 1991, Dureman & Sälde 1959).

In Study III and IV, psychomotor speed was measured by Trail making A and executive function by Trail making B. An easily administered test of scanning and visuomotor function (speed and attention), and cognitive flexibility was given in two parts. In Trail making A, the subject drew lines to connect numbered circles on a work sheet (numeric order). In Trail making B, the same numbered circles and lettered circles were connected in alphabetic order. Subjects were urged to connect the circles “as fast as they could” (Hom & Reitan 1984, Reitan 1992).

Visual-spatial perception/construct and memory

Rey Ostereich Complex Figure (ROCF) is a test of visual-spatial perception, and construct and memory. The immediate and delayed recall conditions are a test
Material and methods

of incidental or implicit memory (Osterrieth 1944). The Rey Ostereich Complex figure was used in study II and III. Examinees had to reproduce a complicated line drawing on a paper, first by copying and then from memory (immediate recall and delayed recall). Each copy was scored for accurate reproduction and placement of 18 specific design elements. In the second part, the subjects were asked to reproduce the figure from memory after 15 minutes. The examinees were not told beforehand that they would be asked to draw the figure from memory.

Episodic memory

Episodic memory is the memory of autobiographical events (times, places, associated emotions, personal, contextual knowledge) (Babcock & Salthouse 1990). Episodic memory was examined in study I and II, and was measured by 1. Prose Recall test (Swedish version of the Logical Memory in the Wechsler memory Scale), in which the participants were asked to immediately recall a brief story of 100 words. The results were coded for the amount of information recalled. 2. Thurstone’s Picture Memory test, which is a non-verbal memory test. Participants were shown 28 drawings and then asked to point them out among other drawings. 3. Memory-in-Reality (MIR) test is a delayed (30 min) free recall test of 10 objects (Wechsler 1991, Thurstone & Thurstone 1949, Johansson 1988/89). In Study III and IV, the test Memory of a story was used for measuring episodic memory. A short story was read (the story is like a news telegram or press item from the radio or television), and the examinees had to recall the story immediately afterwards. After 20 minutes, the same test was performed to recall the same story (Babcock & Salthouse 1990).

Semantic memory

Semantic memory concerns the factual information and general knowledge about the world that we, for example learnt at school (Tulving 1972). Semantic memory was measured in study I and II by 2 tests 1. The Swedish version of the information task, consisting of 22 general knowledge questions and 2. Verbal Meaning test, in which participants were asked to identify a synonym to a target word. The test consists of two parts of 15 words each (Johnsson & Molander 1964, Dureman & Sälde 1959). In study III and IV, semantic memory was measured with Word knowledge test. The examiner received a paper with a total of 30 words and choose between five examples where one word had the
same meaning as the word to the left. The maximum score is 30 if the words are paired correctly in no more than 7 minutes (Dureman 1971).

**Short-term memory**

The short-term memory includes the episodic buffer-attentional effort, the memory is mostly not permanent, but linking information across domains, with visual, spatial and verbal information (Baddeley 1974, Wechsler 1991). This was measured in study I by Digit Span. The participant had to repeat a sequence of numbers in the same order as previously presented (Digit span-forward). In the Digit span-backward test, digits had to be repeated in reverse order.

**Spatial Performance**

Spatial performance was measured with the Block Design test in study I, III and IV. Block design measures spatial performance and problems in this area include difficulty in copying designs, making constructions and matching or discriminating patterns or faces (Benton & Hécaen 1970). The participant was presented with red and white blocks and cards with different patterns. They then had to reproduce seven patterns with the blocks as quickly as possible (Dureman & Sälde 1959). Each pattern had a maximum score of 6.

**Dementia screening test**

Draw a Clock is one part of a test used in study II. The task requires attention and concentration, numerical sequencing, visual-spatial analysis, execution, and abstract conceptualisation and planning (Goodglass & Kaplan 1983). It is often used in brief cognitive assessments when screening for Alzheimer’s disease and other types of dementia (Lezak et al. 2004). A maximum score of 5 can be achieved. If dichotomised, a score of 4-5 is considered to represent normal cognition, while 0-3 indicates cognitive impairment. The Draw a Clock test has demonstrated good inter-rater reliability (McDowell I 1996).
Table 3. Overview of neuropsychological instruments in study I-IV. Taxonomy of the memory describing cognitive tests see Figure 1.

<table>
<thead>
<tr>
<th></th>
<th>study I</th>
<th>study II</th>
<th>study III</th>
<th>study IV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Global cognitive screening test</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Mini Mental State Examination</em></td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td><strong>Psychomotor speed and executive function</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Perceptual speed</em></td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Symbol digit</em></td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Trailmaking A</em></td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Trailmaking B</em></td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Visuospatial performance</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td><em>Block Design</em></td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td><strong>Visual-spatial perception construct and memory</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Rey Ostereich Complex Figure</em></td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Episodic memory</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Prose Recall</em></td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Thurstone’s Pictures</em></td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Memory-in-Reality</em></td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Memory of a Story</em></td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Semantic memory</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Information task</em></td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Verbal meaning</em></td>
<td>x</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><em>Word knowledge</em></td>
<td>x</td>
<td>x</td>
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<tr>
<td><strong>Short-term memory</strong></td>
<td></td>
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<tr>
<td><em>Digit Span Forward</em></td>
<td>x</td>
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<td></td>
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<tr>
<td><em>Digit Span Backward</em></td>
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<td></td>
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<tr>
<td><strong>Dementia screening test</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Draw a Clock</em></td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Material and methods

Assessment of sleep

Insomnia

Insomnia was measured with the Minimal Insomnia Symptom Scale consisting of 3 items focusing on difficulties initiating sleep, difficulties maintaining sleep and non-restorative sleep (Broman et al. 2008). The patients graded their difficulties on a scale ranging from no problems (0), to very great problems (4). Using a summation score, insomnia can be sub-grouped as no insomnia (0-3), subclinical insomnia (4-6), moderate insomnia (7-9) and severe insomnia (10-12). Results have shown that MISS possesses adequate reliability and validity among elderly patients (Hellstrom et al. 2010).

Excessive daytime sleepiness

Excessive daytime sleepiness was measured with the Epworth Sleepiness Scale consisting of 8 items that describe different daily situations of daytime sleepiness. The patients were asked to rate the likeliness of dozing off or falling asleep. Each situation was rated on a scale of 0-3, where high scores indicate a greater propensity to fall asleep. The total score is 24, with a cut off >10 indicating excessive daytime sleepiness (Johns 1991). The instrument has shown good validity and reliability across different age groups and populations (Ulander et al. 2010).

Sleep disordered breathing

Polysomnography is the standard diagnostic test for sleep apnea, but it needs sleep laboratories and sleep specialists for diagnostic evaluation (Flemons et al. 2004). One night’s sleep was measured in study III and IV with an ApneaLink which is a simple respiratory recording screening tool, used as a first identification of SDB. A full night’s respiratory recordings can be performed in the patients’ homes using a portable two-channel screening tool (ApneaLink device, ResMed Corporation, Poway, CA, USA). ApneaLink measures airflow through a nasal cannula connected to a pressure transducer and pulse oximetry. Apnoeas and hypopneas are automatically scored by the ApneaLink software and an AHI is provided based on recording time. Validation of the ApneaLink demonstrates that the device provides reliable information regarding AHI, when compared with a full polysomnography (Erman et al. 2007, Nigro et al. ...
Material and methods

2013). SDB was dichotomised into two groups; no SDB (AHI <15/hour of sleep) and SDB (AHI ≥15/hour of sleep).

Sleep and wake pattern

To register one week of the patients’ sleep and wake pattern, an actigraphy can be used (SenseWear BMS Pro 2, BodyMedia Inc, Pittsburg, PA, USA). The SenseWear BMS is a simple, wireless device that is worn on the upper right arm under the clothing for continuous data collection. The tool reveals more fragmented sleep than polysomnography (Ancoli-Israel et al. 1991).

Assessment of self-care

The European Heart Failure Self-Care Behavior Scale (EHFScB-9)

The European Heart Failure Self-Care Behavior Scale is a 9-item scale that utilises a 5-point Likert scale between 1 (I completely agree) and 5 (I completely disagree) to measure self-care behaviours that are advocated by guidelines (McMurray et al. 2012) and guidance (Lainscak et al. 2011) documents for HF treatment and care. Overall score ranges between 9-45, where lower scores indicate better self-care behaviour. The scale has been found to have satisfactory reliability and validity, Chronbach’s alpha varied between 0.68 and 0.87 in different countries. The EHFScB-9 measures different construct than quality of life (r 0.18) and adherence (r 0.37)(Jaarsma et al. 2009).

Statistical analysis

For all studies (study I-IV), descriptive statistics were used to describe the study variables and population. Continuous data were described with means and standard deviations, and categorical data were described with median and quartiles, or as frequencies and percentage. Differences between the groups were tested with Student’s t-test or Mann-Whitney U test depending on the level and distribution of data. Categorical data were analysed with Pearson’s chi-square test. The statistical packages used for the data analysis were SAS Proc Mixed multilevel modelling (SAS Institute 2002-2003) and SPSS
version 16.0 (SPSS Inc., Chicago, IL, USA)(study I-II), SPSS version 20.0 (SPSS Inc., Chicago, IL, USA) (study III) and STATA 12 (Stata Corp, college station, TX, USA) (study III-IV). The level of statistical significance was p< 0.05 (study I-IV).

Model building in Study I and II
The Generalised Estimation Equations (GEE) were performed in these studies. The GEE model is conceptually equivalent to regression analysis, but it is used to control for the clustering of twins within a pair as independence in twin pairs could not be assumed (monogyotic twins look alike). GEE was performed using SAS Proc Mixed (SAS Institute 2002-2003).

Study I
In study I, GEE was used to produce a latent growth curve model in order to measure change over time. Latent growth models measure a trajectory of decline across the entire sample. A phenotypic latent growth model with a full maximum-likelihood estimate technique was used in the growth models (McArdle et al. 2002, McArdle & JR 2003). Both linear and quadratic models were considered. Model 1 included interaction terms between linear and quadratic age and HF, model 2 included sex, age, educational level, and diabetes and model 3 sex, age, educational level, arterial hypertension, diabetes and smoking, excluding individuals with dementia. To allow for comparison between cognitive tests (different scores and number of questions in each instrument), all scores were standardised into t-score (mean 50, SD 10) (Streiner 2008).

Study II
The GEE was used as a logistic regression with multilevel modelling on all types of dementia, vascular dementia, and Alzheimer’s disease, to analyse factors from models related to an increased risk of dementia. In the first model, gender, age, educational level, waist circumference, diabetes, hypertension, smoking and depression were entered as covariates, whereas model 2 also controlled for creatinine, urea, urate and homocysteine.

Study III
Multiple linear regression analyses were conducted to investigate if SDB and insomnia were associated with cognitive functioning. For the models, well-known factors associated with cognitive function were included as covariates. These covariates were sex (male), age, education (university degree), BMI,
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BNP, diabetes type I and II and smoking. All regression models were based on robust standard errors as the assumption of normality was violated (not normally distributed data in the instruments (Acock 2008).

Study IV
Correlation analyses were conducted to describe the bivariate relationship between study variables (Spearmans’s rho): self-care (EHFScB-9), cognitive dysfunction (MMSE, Trail making A and B, ROCF, Word knowledge, Memory of a story, Block Design), insomnia (MISS), excessive daytime sleepiness (ESS), symptom severity (NYHA class, BNP) and age. To explore the association between cognitive function and self-care, multiple linear regression analyses, based on robust standard errors, were conducted. In these models, self-care was included as the dependent variable. The cognitive tests were included as independent variables. In all models, age, education, NYHA class II-IV, BNP, insomnia, daytime sleepiness and depression were included as covariates. In study IV a model was developed to test the relation between cognition, sleep, symptoms of depression and self-care, see Figure 4

![Figure 4](image-url)

Figure 4. Sleep and symptoms of depression may function as moderators between cognition and self-care. This hypothesized moderator effect implies that the level of influence cognition has on self-care depends on the level of sleep problems and symptoms of depression.

Table 4 describe all the different variables controlled for in the different models in study I-IV.
Table 4. Factors controlled for in the models for study I-IV.

<table>
<thead>
<tr>
<th></th>
<th>Study I</th>
<th>Study II</th>
<th>Study III</th>
<th>Study IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>x</td>
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<td>x</td>
<td>x</td>
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<tr>
<td>Sex</td>
<td>x</td>
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<td>x</td>
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<tr>
<td>Education</td>
<td>x</td>
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<td>x</td>
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<tr>
<td>Waist circumference</td>
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<td></td>
<td>x</td>
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<tr>
<td>Depression</td>
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<td>x</td>
</tr>
<tr>
<td>BMI&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td>x</td>
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<td></td>
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<tr>
<td>Depression</td>
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<td>x</td>
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<tr>
<td>Diabetes</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Hypertension&lt;sup&gt;b&lt;/sup&gt;</td>
<td>x</td>
<td>x</td>
<td></td>
<td>x</td>
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<tr>
<td>Smoking</td>
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<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>NYHA&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td>x</td>
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<td>BNP&lt;sup&gt;d&lt;/sup&gt;</td>
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<tr>
<td>Creatinine</td>
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<td>Urea</td>
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<td>Urate</td>
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<tr>
<td>Homocysteine</td>
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<td>AHI&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Time below &lt;90%</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia&lt;sup&gt;f&lt;/sup&gt;</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excessive daytime sleepiness&lt;sup&gt;g&lt;/sup&gt;</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: <sup>a</sup>BMI-Body Mass Index, <sup>b</sup>hypertension- >140/90, <sup>c</sup>NYHA-New York Heart Association, <sup>d</sup>BNP- B-type natriuretic peptide, <sup>e</sup>AHI-Apnoea-Hypopnoea Index, <sup>f</sup>Insomnia- The Minimal Insomnia Scale, <sup>g</sup>Excessive daytime sleepiness-The Epworth Sleepiness Scale
Materials and methods

Ethical considerations

Ethical principles of clinical research, i.e., autonomy, beneficence, non-maleficence and justice (Beauchamp 2009), guided these studies and were followed throughout the thesis. All studies have been planned and conducted in accordance with the declaration of Helsinki (World Medical Association Declaration of Helsinki 2002). In study I and II, the population-based sample consisted of participants from the longitudinal OCTO-twin study (McClearn et al. 1997) that was approved by the Regional Ethical Review Board in Stockholm, Sweden.

The study protocol for study III and IV was approved by the Ethics Committee at the faculty of Health Science, University of Linköping (registration number M222-08T81-09). All patients included in study III and IV received both verbal (by phone and by the first meeting with a nurse) and written information before giving written consent to participate. They were also informed that their participation was voluntary, that they could withdraw at any time and that the information they provided would be treated confidentially.

No extra interventions were performed in connection with the studies and therefore there were no extra risks for the patients when accepting to participate. Patients’ integrity has been respected through the coded and confidentially handled questionnaires, and all data are presented on a group level. The respondents in this thesis were treated as vulnerable according to criteria of old age and disease severity. Some of the patients had impaired cognitive functioning, but not all respondents were vulnerable according to those criteria. The participating patients in the study benefited from an extra health check-up and having a contact person. The negative aspects could be having to fill in all questionnaires, having an actigraphy (Ancoli-Israel et al. 2003) on the arm for one week and measuring sleep and wake pattern for one night with an ApneaLink (Erman et al. 2007).
RESULTS

Study I

Longitudinal changes in cognition among individuals 80 years of age and older with HF (I)

This study explores longitudinal changes in cognition among HF patients above 80 years of age. At baseline, 95 patients of 702 had HF whereas 511 were non-HF patients. The HF patients had significantly more comorbidities, such as angina pectoris, higher prevalence of myocardial infarct, stroke and vascular dementia. They also had significantly higher laboratory values, such as creatinine and urea and used more diuretics.

The different covariates controlled for in the models (1, 2, 3) were sex, age, educational level, arterial hypertension, diabetes and smoking. Model 1; no covariates, model 2; sex, age, educational level, diabetes, model 3; sex, age, educational level, diabetes, arterial hypertension and smoking.

In the longitudinal observations, HF patients showed a lower mean performance in spatial performance measured with the Bock Design test (including model 2 and 3), both when dementia cases were included or excluded. Longitudinal changes were also found in episodic memory between HF and non-HF patients measured with Thurstone picture and Prose recall.

There were different results when dementia cases were included or excluded. There were no changes in logic memory using Prose Recall (including model 1, 2 and 3) when excluding the dementia group and using the same models and the battery of neuropsychological test. The non-verbal test measured with Thurstone picture showed longitudinal decline when model 2 was included. The Digit span forward test recalling Short-term memory showed differences when dementia cases were included. The study describes that individuals with HF scored significantly lower in spatial abilities and episodic memory.

The result is compared to a healthy control group and dementia factors have been considered, see Figure 5.
**Study II**

**Risk of dementia in congestive heart failure patients aged 80 and older**

In the second measure (IPT 2), 138 patients out of a total of 702 patients aged 80 years or above had HF whereas 564 did not. The HF population had significantly more comorbidities, such as angina pectoris, higher prevalence of myocardial infarct, stroke and vascular dementia. They also had significantly higher laboratory values, such as creatinine, urea, urate, homocysteine and more use of diuretic medications. The prevalence between the HF and non-HF of the different dementia diagnoses are showed in Figure 6.

![Diagram showing the relationship between age, cognitive decline, and dementia diagnoses]

**Figure 5.** Summary of the result from study I.

**Figure 6.** Prevalence of dementia diagnoses among HF and non-HF patients.
The result showed that the HF group had significantly higher prevalence of vascular dementia and all types of dementia than that without HF. In this group, no factors were associated with Alzheimer's disease. Neither were sex, age, education levels, waist circumference, smoking, creatinine, urea or urate found to be significant to any dementia diagnoses in this population. The prevalence of dementia was higher among individuals with HF, and depression and hypertension were significantly associated with a risk for all types of dementia. Increased levels of homocysteine were found to be a marker of all types of dementia in HF patients, and diabetes was related to greater risk for vascular dementia in HF patients > 80 years of age (see Figure 7).

**Figure 7.** Summary of the result from study II.
Study III

Association between sleep disordered breathing, sleep and wake pattern and cognitive impairment among patients with chronic heart failure (III)

This study included 137 HF patients with a median age of 72 years (68% male and 58% female) in NYHA class II.

The result from this study showed that the patients with SDB (full ApneaLink data) had significantly higher AHI, lower saturation and a higher saturation time below 90%, more difficulties maintaining sleep and lower levels of daytime sleepiness, compared to the patients with non-SDB (see Table 5). Of the total sample, 30 patients had missing data in the ApneaLink. These were older and had more disease severity according to NYHA class III (53%), and had significantly higher creatinine values compared to the patients with full ApneaLink data (n=107). Cognitive function and sleep and wake patterns did not differ between the SDB and non-SDB group.

The regression analysis showed that insomnia measured with MISS, was the only factor associated with a decreased global cognitive function.

The regression analysis showed that higher age was associated with decreased executive function, visual-spatial perception and spatial performance. Higher education levels were important for improving global cognitive function and semantic memory. Smoking was related to impaired semantic and episodic memory. Factors that did not have any significance were AHI, saturation time below 90%, daytime sleepiness, sex, BMI, BNP and diabetes. The prevalence of cognitive dysfunction was low, 78% had normal cognitive function. Half of the patients suffered from SDB, and difficulties to maintain sleep and excessive daytime sleepiness were associated with SDB. Insomnia was the only sleep-related factor significantly influencing cognition.
Table 5. Objective and subjective measures of breathing events, sleep and wake pattern, insomnia and excessive daytime sleepiness in chronic heart failure patients with and without sleep disordered breathing (SDB).

<table>
<thead>
<tr>
<th></th>
<th>Full ApneaLink in all patients (N=107)</th>
<th>No SDB (n=60)</th>
<th>SDB (n=47)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHI Md (Q1-3)</td>
<td>13(5-25)</td>
<td>7(3-11)</td>
<td>26(21-37)</td>
<td>&lt; .001*</td>
</tr>
<tr>
<td>Lowest saturation Md (Q1-3)</td>
<td>85(78-88)</td>
<td>87(83-89)</td>
<td>80(74-85)</td>
<td>&lt; .001*</td>
</tr>
<tr>
<td>Time below saturation &lt;90% Minutes Md (Q1-3)</td>
<td>4(1-15)</td>
<td>1(1-7)</td>
<td>9(3-27)</td>
<td>.003*</td>
</tr>
<tr>
<td>MISS Md (Q1-3)</td>
<td>4(2-7)</td>
<td>4(2-6)</td>
<td>5(3-8)</td>
<td>.199*</td>
</tr>
<tr>
<td>MISS 4 categories</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No insomnia n (%)</td>
<td>35(33)</td>
<td>24(40)</td>
<td>14(30)</td>
<td>.486 b</td>
</tr>
<tr>
<td>Subclinical insomnia n (%)</td>
<td>38(35)</td>
<td>20(33)</td>
<td>18(38)</td>
<td></td>
</tr>
<tr>
<td>Moderate insomnia n (%)</td>
<td>26(24)</td>
<td>12(20)</td>
<td>14(30)</td>
<td></td>
</tr>
<tr>
<td>Severe insomnia n (%)</td>
<td>6(6)</td>
<td>5(8)</td>
<td>1(2)</td>
<td>.710 b</td>
</tr>
<tr>
<td>DIS n (%)</td>
<td>39(36)</td>
<td>23(38)</td>
<td>16(34)</td>
<td>.046 b</td>
</tr>
<tr>
<td>DMS n (%)</td>
<td>72 (67)</td>
<td>36(60)</td>
<td>36(76)</td>
<td></td>
</tr>
<tr>
<td>NRS n (%)</td>
<td>56(52)</td>
<td>28(47)</td>
<td>28(59)</td>
<td>.149 b</td>
</tr>
<tr>
<td>ESS totalscore Md (Q1-3)</td>
<td>9(6-11)</td>
<td>9(6-12)</td>
<td>8(5-12)</td>
<td>.590 *</td>
</tr>
<tr>
<td>EDS n (%)</td>
<td>45(42)</td>
<td>27(45)</td>
<td>18(38)</td>
<td>.001 b</td>
</tr>
</tbody>
</table>

* Mann Withney U test, b Chi-square test.

Note: No SDB (AHI<15) and SDB (AHI≥15). AHI-Apnoea-Hypopnoea Index, MISS - The Minimal Insomnia Symptom Scale, DIS- Difficulties Initiating Sleep, DMS- Difficulties Maintaining Sleep, NRS- Non Restorative Sleep, EDS-Excessive Daytime Sleepiness, ESS- The Epworth Sleepiness Scale.
Study IV

The relation between self-care and cognitive dysfunction in patients with chronic heart failure (IV)

In this study, a total of 142 individuals with HF, median age of 72 years were included. Of these, 68% were male, most of them in NYHA class II (58%), and III (35%). Disease severity measured with Charlson co-morbidity index showed that 82% were in level and assigned weight of 1 to 2, BNP showed a median value of 140.

The bivariate correlation between self-care (EHFScB-9), cognitive test battery, age, education, NYHA class, BNP, insomnia, daytime sleepiness and depression, showed that only psychomotor speed was significantly correlated with self-care ($r_s = .21$, $p< .05$). None of the other study variables correlated significantly with self-care, except depression ($r_s = .23$, $p< .05$). Age, education, NYHA, BNP and daytime sleepiness were significantly correlated with cognitive function. The robust linear regressions showed that slower management in psychomotor speed was the only cognitive test that had significant association with self-care. Other variables associated with self-care behaviour were NYHA class and symptoms of depression. Neither age, education, BNP, insomnia or daytime sleepiness were significantly associated with self-care in any of the regression models.

In the moderator test, no interaction effect was demonstrated for any of the moderator variables in combination with cognitive function and self-care. Neither sleep disturbance nor depression moderated the relation between cognitive function and self-care.

Psychomotor speed was the only dimension of cognitive function associated with self-care measured with the EHFScBS-9. The level of psychomotor speed has implications for how patients should be educated and supported to perform self-care.
DISCUSSION

This thesis presents several new and clinically important findings regarding cognitive dysfunction in patients with chronic HF. In contrast to several other studies in HF patients, cognitive function in this thesis was evaluated with a battery of neuropsychological tests measuring global cognitive dysfunction, psychomotor speed, executive function, visual-spatial perception/construct, spatial performance, and semantic and episodic memory. The prevalence of cognitive decline over time was found to be more prominent among patients >80 years of age with HF compared to those without HF, especially with regard to spatial ability and episodic memory (I). Spatial problems and episodic memory have implications for everyday life and may lead to decreased adherence to prescribed therapy and self-care management. When looking specifically at the relation between cognition and self-care in elderly individuals with HF, psychomotor function (speed and attention) was the only dimension of cognitive function significantly associated with self-care (IV). Psychomotor speed has implications for how patients should be educated and supported to perform self-care. A decrease in sustained attention and ability to carry out more than one task at the same time could lead to difficulties performing self-care. Furthermore, dementia was found to be more prevalent in the oldest-old >80 years of age with HF compared to those of the same age without HF (II). Diabetes, hypertension and depression were factors associated with an elevated risk for developing dementia among patients with HF and a high level of homocysteine was viewed as a marker for developing dementia when suffering from heart failure. In this thesis, sleep was also hypothesised to influence cognitive function in HF. However, insomnia was the only sleep-related factor influencing cognition among elderly individuals with HF (III).

Prevalence and progression of cognitive dysfunction in heart failure
Cognitive dysfunction has been reported in patients suffering from a variety of cardiovascular disorders. It is well documented after coronary artery bypass graft surgery (Ahlgren et al. 2003, Ho et al. 2004), and among survivors of sudden cardiac arrest (Nunes et al. 2003). Only a limited number of clinical studies have systematically assessed cognitive performance in HF patients (Vogels et al. 2007b, Pressler 2008), and mild cognitive impairment exceeds the prevalence of dementia range from 53% to 58% in older patients with mild to
moderate HF (Zuccala et al. 1997), and 25% to 58% cognitive impairment (Pressler 2008, Bennett S. 2003, Vogels et al. 2007b). The cognitive areas commonly assessed are memory, attention, problem solving and motor speed (Vogels et al. 2007b). A study by Pressler and colleagues in 2010 showed that HF patients have poorer memory, psychomotor speed and executive function compared to healthy controls. Men with HF had poorer memory, psychomotor speed and visuospatial recall ability than women (Pressler et al. 2010b). Very few studies have examined the visual/spatial construction domain (Bauer et al. 2011), or the episodic memory which is used as a diagnostic marker to detect early front temporal dementia caused by Alzheimer’s disease (Hornberger & Piguet 2012). In this thesis individuals with HF 80 years of age and older, showed a decline in both spatial and episodic memory when compared to healthy controls (I).

Screening for cognition or dementia can be done with a MMSE test. The cut-off score for mild cognitive decline is a MMSE score of 25 to 27 and the cut-off for dementia is MMSE ≤24 (Folstein 1975). Montreal Cognitive Assessment (MoCa), is more sensitive to mild cognitive dysfunction, the cut-off score for cognition/dementia is a MoCa score of 23 to 26, which represents mild cognitive dysfunction. A score ≤ 23 represents severe cognitive impairment suggesting dementia (Nasreddine et al. 2005). The MMSE and MoCa are simple screening tests that can assess whether an individual is at risk of cognitive dysfunction. If this is found, further neuropsychological testing is warranted. However, this needs further expertise, while MMSE and MoCa can be administered by a nurse in, for example, a heart failure clinic. If clinical dementia or early stages of dementia are detected, an inhibitor drug can be the solution to delay the progress of Alzheimer’s disease. In people with Alzheimer’s disease, treatment with a cholinesterase inhibitor or memantine (N-methyl-D-aspartate receptor antagonist) may provide symptomatic relief, but does not appear to alter the progression of the illness (Weinreb et al. 2011). There is pharmaceutical treatment for mild cognitive impairment (Russ & Morling 2012), but there is no convincing evidence of the benefit (Flicker et al. 2012). Those with mild cognitive impairment are at increased risk of dementia, but on the other hand, most older people with memory loss do not have dementia (Flicker et al. 2012).

The prevalence of dementia was higher among individuals with HF (II). This thesis showed that predictors affecting dementia in HF patients aged 80 and older were diabetes, depression and hypertension. High levels of homocysteine were also found to be a marker for dementia. Early
identification of dementia and predictors that affect this condition is important in order to provide effective treatment of the symptoms and preventive care. Preventive actions could include good metabolic control in diabetes patients and regular blood pressure check-ups to prevent and treat hypertension. Knowledge about that depression appears with different co-morbidities, and that depression is a factor commonly discussed to have impact on both normal sleep and cognitive function among older adults is of importance (Johansson et al. 2012).

Sleep-related factors and cognitive function in elderly individuals with heart failure
Forty-four percent of the patients had SDB (AHI ≥15) in study III. The SDB group had significantly higher saturation time below <90%, more difficulties maintaining sleep and lower levels of daytime sleepiness compared to the non-SDB group. Cognitive function and sleep and wake patterns did not differ between the SDB and the non-SDB group. Insomnia was associated with decreased global cognition.

The prevalence of cognitive dysfunction was low in this sample with predominantly mild to moderate CHF. This might have influenced the lack of associations between cognitive function and SDB. Insomnia was the only sleep-related factor significantly influencing cognition. High prevalence of insomnia is not necessarily predicted by age itself. Insomnia is associated with comorbidities such as depression, somatic health problems and the risk of dementia in connection with using hypnotics in patients with insomnia (Buysse 2013, Chen et al. 2012). Insomnia is prevalent in patients with chronic disease, including HF, and is a significant contributing factor to fatigue and poor quality of life. The pathophysiology of HF often leads to fatigue due to nocturnal symptoms that cause sleep disruption, including cough, orthopnea, paroxysmal nocturnal dyspnea, and nocturia (Hayes et al. 2009).

Cognition and self-care in heart failure
Study IV, describes the relationship between self-care and cognitive function with an extended neuropsychological battery of cognitive tests and known patient-related and independent factors affecting patients with chronic heart failure. Self-care was measured with the validated EHFScBS (Jaarsma et al. 2003).

The result showed that sleep, daytime sleepiness, disease severity and age were not directly associated with self-care. Psychomotor speed measured with Trail making A, a test of scanning, and visuomotor function (speed and
attention) were the only dimensions of cognitive function associated with self-care (B=-0.07, t (1) = -2.35, p<0.05). Only one of seven cognitive tests had a significant association with self-care. What can explain these findings? Was it due to the study population not having severe HF, few comorbidities and a median age of 72 years? Was the instrument measuring self-care not sensitive enough? Further studies in this field are needed to answer these questions.

The level of psychomotor speed has implications for how patients should be educated and supported to perform self-care. A decrease in this function could lead to difficulties in sustained attention, the ability to carry out more than one task at the same time and alternating attention from one task to another. Low psychomotor speed influences the ability to think fast and the attention for receiving information on self-care may be affected. Screening for psychomotor speed and individualising self-care education is advocated among patients with heart failure.

Self-care is the practice of activities that individuals initiate and perform on their own behalf to maintain life, health and wellbeing, i.e. activities to live and survive. It is an active phenomenon that requires people to observe their health condition and use decision-making skills in order to choose an appropriate course of action (Orem 1991, Cavanagh 1991). Decisions about symptoms, daily decision-making (Dickson et al. 2007, Riegel et al. 2010) and abilities to learn and adapt to self-care management (Stromberg et al. 2006) is a daily challenge for HF patients.

A patient who suffers from dementia, regardless of the type of dementia, cannot fully understand their health condition and decision-making regarding a course of action and it is more difficult with worsening dementia. Nurses, other healthcare professionals and family caregivers can help the patient to stabilise comorbidities such as diabetes or hypertension, and help with medications and symptom monitoring etc.

The middle-range theory describes self-care in chronic illness and that all healthcare professionals have a role in promoting self-care. The middle-range theory by Riegel et al, measures self-care maintenance involving physical and emotional stability (Riegel et al. 2012). Individuals with dementia need help in this area, but those with a decline in spatial, episodic memories and psychomotor speed should not experience any major difficulties with maintenance.

For those with a decline in speed and attention (psychomotor speed), behaviours related to lifestyle could be a problem, for instance preparing healthy food, or coping with stress. For individuals with a decline in spatial
and episodic memory who take medications as prescribed, self-care maintenance may not be a problem as long as their behaviour mirrors healthcare professionals recommendations. Insomnia can result in daytime sleepiness, which could cause depression when the patient does not have the fortitude to maintain good physical and emotional status. Adherence is an essential component of self-care maintenance, and adherence to therapies is associated with the best outcomes (Riegel et al. 2012).

The self-care monitoring process is to observe oneself for changes in signs and symptoms, vigilant body monitoring, surveillance and body listening (Dickson et al. 2008). The goal of self-care monitoring is the recognition that a change has occurred. A decline in episodic memory could cause problems in symptom monitoring and for having a decline in spatial performance (room orientation, understanding drawings, remembering faces/patterns, memories) could telemonitoring be difficult to deal with.

A decline in psychomotor speed, visualmotor speed and action could be troublesome in stressful situations. Visual and hearing problems could give a decline within appropriate attention (Lin et al. 2011, Dillon et al. 2010).

Self-care management is a process of recognition of changes in signs and symptoms, decision-making about self-care actions, and evaluation of the outcomes of an action. This area is dependent on an intact memory. Early dementia cases can have trouble performing adequate self-care management. A decline in the episodic memory and spatial performance recognition of signs and symptoms could have associations to this area because individuals do not remember what action they should perform. The visual orientation to describe a pattern and a decline in the spatial area could be troublesome. Decision-making and evaluation of the outcome of an action requires intact memory, personal skills, and experience of this action. Individuals need to be able to mentally simulate options and decide on a course of action. The assessment of attention to the effectiveness of a treatment in order to evaluate whether that specific approach should be tried again in the future, those actions might not be appropriate in individuals with a dementia diagnosis or who have experienced a decline in episodic and spatial performance.

The management of symptoms involve cognitive decision-making in response to signs and symptoms (Riegel et al. 2000). Symptom management involving cognitive decision-making is a theory with analytical and systematic methods of weighing evidence before selecting a course of action, but patients do not use those methodical, rational decision-making processes (Riegel et al. 2012).

Adults with HF who have a mild cognitive dysfunction with other affecting problems are also a vulnerable patient group, and in need of interventions in
HF self-care management (Lee et al. 2012). Managing self-care is important because we know that structured patient education that focused on self-care can reduce mortality and morbidity among HF patients (Stromberg et al. 2003, McAlister et al. 2004).

Methodological considerations

Design and samples
We used a quantitative design in this thesis. The advantage of the quantitative design is that it is possible to measure outcomes in a larger group of study participants and carry out statistical analyses of the data including comparisons and correlations. It also gives the possibility to generalise the findings. By contrast, a qualitative design produces detailed information in a smaller number of people, which could increase the depth of understanding of the research questions and a deeper understanding of the people and situations studied. However, generalizability becomes limited (Patton 2002).

In study I and II we have used data from a population-based prospective longitudinal design with individuals aged 80 years and older and an extensive battery of neuropsychological tests which is strength in these studies. Few studies have had a longitudinal design including patients 80 years and older. The data in study I and II were collected between 1991 to 2002 and great changes in diagnostics and treatment have been made since then. The study population in these studies was not diagnosed with echocardiography, their medical treatment were diuretic and digitalis in contrast to modern heart failure treatment, such as beta blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers and mineralocorticoid receptor antagonists. Consequently, the study population in study I and II also had fairly high blood pressure compared to current medical recommendations. It is therefore interesting to speculate whether the oldest-old of today have a better prognosis with regard to their cognitive status.
It was a challenge to perform longitudinal measurements for 10 years in an older twin population that includes both a HF and a non- HF group. For example to deal with deaths and developing HF. Another challenge was the use of specific statistical methods to control for the twin population as individuals but also in twin pairs. We also had to control for the development of dementia over time.
Study III and IV had a cross sectional design. Cross sectional design is useful for description or investigations of relationships and it is valuable for generating theories or hypotheses for future research. Data for the cross-sectional studies were collected at the same time, the limitation being that we could not measure over time (Polit 2004). This design also emphasises that the sample is representative of the population as the characteristics of the sample may affect the factors investigated (Altman 1991). To make the result possible to generalise, the sample should be randomly selected (Martin 2005). The representative sample in study III and IV in this thesis was recruited from one university hospital and two county hospitals in the south of Sweden. It consisted of patients living in the community-dwelling HF patients who were recruited after discharge from outpatient clinics. This selection from three hospitals should increase the representativeness of the population and make the results possible to generalise.

Study III and IV, had a rather healthy population in NYHA class II-III, with not so many symptoms of heart failure and cognitive dysfunction. Patients in severe NYHA classes III-IV are unfortunately less likely to accept participation in a complex study like this one, when they not have strength to complete tests and fill in all assessments. This study included a battery of instruments and a neuropsychological test battery, SenseWear actigraphy for one week, ApneaLink for one night, to measure flow limitation and snoring with a nasal cannula in the nose, and a saturation sensor connected to the finger. Those who did not perform the measurement with the ApneaLink stated that the nasal cannula was claustrophobic, or that they could not manage the technical issues (cognitive and pre-dementia patients). With regard to measurements by SenseWear, 100% managed to use the equipment, but a few did not complete their registrations (less than 7 days).

Data collection
In contrast to several other studies in patients with heart failure, cognitive function in this thesis was evaluated with a battery of neuropsychological tests measuring global cognitive dysfunction, psychomotor speed, executive function, visual-spatial perception/construct, spatial performance, and semantic and episodic memory. The choice of instrument and to measure cognitive dysfunction has been to “think broad” and as thought to be comparable data in the four studies with the same neuropsychological test battery. The first study (Hjelm et al. 2011) showed that the oldest-old patients >80 years of age performed lower within spatial performance measured with Koh’ Block Design
(Dureman & Sälde 1959). Therefore, we used two tests in study III and IV, Block Design measuring spatial performance (Dureman & Sälde 1959), and Rey Ostereich Complex Figure (ROCF) (Osterrieth 1944) measuring visual-spatial perception/construct and memory. The first study also showed that episodic memory measured with the Prose Recall and Thurstone Picture test (Thurstone & Thurstone 1949, Wechsler 1991) declined over time in the oldest-old HF patients. Two tests were performed, but it was Prose Recall that declined over time. In study II and IV, we received help from a neuropsychologist to collect similar original tests from the OCTO-twin study as in the first studies (Cederlof & Lorich 1978). The tests needed to have the quality that different nurses could learn to execute and handle them in research.

To measure sleeping disorders, we chose to use the well validated Minimal Insomnia Symptom Scale (MISS) (Broman et al. 2008). It consists of three items focusing on difficulties initiating sleep, difficulties maintaining sleep and non-restorative sleep. The Epworth Sleepiness Scale (ESS) (Johns 1991) was used to measure daytime sleepiness (EDS). These instruments are easy for the patients to fill in, they do not contain too many questions and they provide us with answers to our research questions. Another instrument that we could have considered using for measuring insomnia is the Uppsala Sleep Inventory (Mallon & Hetta 1997) which measures sleep variables, bedtime, sleep onset latency, nocturnal awakenings, morning awakening time, sleep duration, assumed sleep duration, numbers and duration of naps, if the patients “sleep to little” (yes/no) and use of hypnotics. Another instrument for subjective measurements is the EDS Stanford Sleepiness Scale (Curcio et al. 2001, Cluydts et al. 2002) or the Sleep-Wake Activity Inventory (Rosenthal et al. 1993).

There are several depression instruments that could be useful in research, from categorical to dimensional instruments. We chose a dimensional instrument, the PHQ- The Patient Health Questionnaire 9 item (PHQ-9), which is based directly on the Diagnostic and Statistical Manual Fourth Edition (DSM-IV). The PHQ-9 has showed good diagnostic validity (Kroenke et al. 2002).

For measuring self-care, we used the European Heart Failure Self-Care Behavior Scale (EHFScB-9). This is a 9-item scale utilising a 5-point Likert scale ranging from 1 (I completely agree) to 5 (I completely disagree) that measures self-care behaviours in relation to CHF. Overall score ranges between 9-45, lower scores indicate better self-care behaviour. The scale measuring self-care behaviors has been found to have satisfying reliability and validity (Jaarsma et al. 2009). Another choice could have been the Self-Care Heart Failure Index
(SCHFI) (Riegel et al. 2009), a tool composed of three sub-scales; maintenance, management, and confidence. However, there is no validated Swedish version of the SCHFI.

**Statistical analyses**
In the analysis missing data in the material was handled, especially in the later measurement (IPT 4-5). The missing data were greater in the HF patients, maybe indicating an even higher cognitive decline in this group.

The extensive neuropsychological test battery had several different test with different scoring. Therefore all scores were standardized into t-score (mean=50, SD 10), which made data comparable. Multilevel models were performed using SAS PROC MIXED multilevel modeling for comparing data with HF and non-HF patients and the deal with independence of twin pairs that could not be assumed (monocytotic twins).

The data were not normally distributed in study III and IV, therefore robust standard errors were conducted using STATA 12 (Stata Corp, college station, TX, USA) in order to prevent type I errors.

The extensive approach among cognitive data increased the missing data (25% missing in performance of all cognitive tests) which is negative, but to have this extensive battery of test in the cognitive area strengths our study results in study III and IV. The sample sizes was limited in some of the regression models, but post hoc power analysis showed that the actual power between the different regression models varied between 0.74 and 0.85 in study IV.

**Generalisability**
This thesis includes four quantitative studies with over almost 850 study participants, some with HF and some used as controls. The thesis has produced result on different aspects of cognitive dysfunction that can be generalised to elderly and the oldest-old patients with HF. However, the generalizability is limited by some factors. In study I and II the diagnosis and treatment regimen has changed during the last decades. In study III and IV finding can only be generalized to stable patients with mild to moderate HF with few co-morbidities.
Clinical implications

- Spatial problems and episodic memory may have implications for everyday life in patients with HF. This might contribute to decreased self-care and less adherence to prescribed therapy and self-care management, and lead to socio-behavioural problems due to an impaired capacity to drive, read and write. Healthcare providers have an important role in identifying these persons and guiding the patient on how to cope with cognitive dysfunction in daily life.

- Early identification of dementia is important for the treatment of HF symptoms and healthcare planning. The prevalence of dementia was higher among individuals with HF. Diabetes, depression and hypertension were significantly associated with an elevated risk of dementia. Increased levels of homocysteine were found to be a marker of dementia in HF patients. Healthcare providers need to be aware of these risk factors for dementia and cognitive decline so they guide and support the patients to improved adherence and prevention, for example understanding the importance of treating an abnormal glucose laboratory value.

- Patients with HF in NYHA class II-III have problems with sustained attention and ability to carry out more than one task at the same time. That could lead to difficulties in self-care.

- In their assessment, healthcare professionals should take into account that cognitive dysfunction may restrain elderly HF patients’ ability to make decisions and perform self-care actions. Patient education strategies should also be adapted to cognitive ability. Staff should listen to the patients and ask questions about how they handle different situations. Patients suspected to have cognitive dysfunction or being at risk of dementia should be given a quick screening test with MMSE or MoCa. If these tests reveal a decline, an expert should be consulted. The MMSE is useful for measuring global cognitive function and as a screening tool for dementia. However, MMSE is less sensitive in assessing mild cognitive dysfunction. In clinical practice both MMSE and MoCa can be too extensive to use. There is a need for a brief, easy to use instrument that is reliable and sensitive to detecting cognitive impairment in HF.
Future research

- This thesis has generated several new research questions where a qualitative design would be appropriate in order to gain a deeper understanding of the field. These include qualitative or mixed method approaches to explore how cognitive dysfunction in patients with heart failure influence their self-care ability and strategies they use to perform self-care.

- To optimally target future intervention more research in the oldest-old >80 years of age is needed regarding cognitive function over time and affecting risk factors.

- Further studies with a prospective and longitudinal design are needed in elderly patients in NYHA class III-IV with more than two comorbidities or multi morbidity, including more long-term diseases.

- The influences of other factors on cognitive dysfunction and dementia such as inflammation, nutrition, use of alcohol and drugs, life stress and social support need to be explored.

- It is necessary to use uniform and sensitive measures to study cognitive function, and it is advised to use the Mini Mental State Examination (MMSE) and Draw a Clock test in HF patients with increased symptom severity (NYHA III-IV).

- More research is needed to with regard to attentional problems affecting self-care among HF patients in NYHA class II-III and screening for psychomotor speed is advocated in future studies.
CONCLUSION

- The prevalence of cognitive decline over time was found to be more prominent in the oldest-old >80 years of age with HF compared to those without HF, especially with regard to spatial ability and episodic memory.

- Dementia, both vascular and all types, was significantly more common in patients above 80 years of age with HF compared to those of the same age without HF.

- Diabetes, hypertension and depression were factors associated with an elevated risk for developing dementia among patients with HF.

- Homocysteine was found to be a marker for dementia in elderly individuals with HF.

- Insomnia was the only sleep-related factor significantly influencing global cognitive function in patients with stable HF with few comorbidities.

- Decreased psychomotor speed was associated with lower self-care in stable HF patients with few comorbidities.

- An extensive test battery to explore different aspects of cognitive function and its relationship to self-care gives more in-depth understanding compared to screening instruments measuring global cognitive function and risk of dementia.

- A decrease in attention capacity could lead to difficulties in self-care performance.
SAMMANFATTNING

Denna avhandling fokuserar på den kognitiva förmågan hos äldre med kronisk hjärtsvikt med fokus på förekomst, riskfaktorer, inverkan av sömn och påverkan på egenvård.

Hjärtsvikt drabbar 1-2% av den vuxna befolkningen i västvärlden. Prevalensen för hjärtsvikt ökar till 10-20% bland individer över 80 år. Hjärtsvikt är associerat med ökad dödlighet och sjuklighet samt en försämrad livskvalitet.

I alla delstudierna användes ett omfattande batteri av neuropsykologiska tester som bedömde kognition inom olika områden: Global kognitiv funktion, psykomotorisk hastighet, exekutiva funktioner, viso-spatial förmåga, spatial förmåga, semantiskt och episodiskt minne.


Den första delstudien handlar om påverkan av hjärtsvikt på förändringar i kognition över tid samt vilka kognitiva funktioner som påverkades av hjärtsvikten. Resultatet visar att individer med hjärtsvikt hade signifikant försämrad spatial förmåga och ett sämre episodiskt minne än de som inte hade hjärtsvikt i samma ålder. Episodiskt minne förändrades även över tid.


Studien handlar om sambandet mellan sömnstörd andning, sömnvakenhetsmönster och kognitiva funktion hos patienter med kronisk hjärtsvikt. De vanligaste sömnrubbningarna hos äldre är sömnstörd andning, svårigheter att somna (insomni), dagtrötthet och störning av drömsömn. Data samlades in från 137 patienter. Totalt 68% var män, medianåldern var 72 år.
och majoriteten av patienterna hade mild-måttlig hjärtsvikt med 58% i New York Heart Association klass II. Resultatet visade att det inte fanns några skillnader i kognitiv funktion och sömnvakenhetsmönster mellan hjärtsviktpatienterna som hade och inte hade sömnstörd andning. Insomni var den enda faktorn som var signifikant associerad med en försämrad kognitiv funktion.

I studie fyra studerades relationen mellan egenvård och kognitiv funktion. Egenvård mättes med The European Self-Care Behavior Scale. Psykomotorisk hastighet dvs. hastighet och uppmärksamhet var den enda kognitiva funktionen som signifikant påverkande egenvård. En försämring i denna funktion kan leda till oförmåga att behålla koncentration att skifera från en övning till en annan, eller att utföra flera övningar vid samma tillfälle. Påverkad hastighet och uppmärksamhet påverkar förmågan att tänka snabbt och uppmärksamheten att ta emot information med egenvårdsuppgifter kan vara påverkad. Det är viktigt att tänka på när egenvårdsutbildning ges till patienter med hjärtsvikt.


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