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Is Sleep Quality related to Cognition in Individuals with Heart Failure?

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Introduction

Heart failure (HF) is a major public health concern. It is associated with frequent hospital admissions¹, poor quality of life², a significant symptom burden³, high morbidity, and increased mortality.^{4–6} Up to half of individuals with HF experience a decline in cognition that does not meet the criteria for dementia, but which is greater than would be expected in normal aging.^{7–9} Among individuals with HF, cognitive impairment has been reported as a significant problem that may also increase morbidity and mortality by diminishing self-management skills.^{5–11} Magnetic resonance imaging (MRI) studies of the brain revealed that individuals with HF present differences in the prefrontal lobe, medial temporal lobe, and hippocampus that are associated with reduced attention, memory, and executive function.^{12–16} These differences in cognition and brain structure may be due to reduced cerebral blood flow arising from low cardiac output.

Cognitive impairment may also be worsened by other factors, such as older age, low education level, depression, medications, and comorbid conditions.^{17,18} While researchers

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have studied several of these variables, the relationship between sleep problems and cognition among patients with HF is still uncertain. Cross sectional studies have documented a relationship between poor sleep quality, excessive daytime sleepiness (EDS), and cognitive function.^{19–24} However, the direction of that relationship is still unclear.

Up to 70% of individuals with HF report problems with sleep^{25–29} and often present with sleep-related breathing disorders (SRBD), such as obstructive sleep apnea (OSA) or central sleep apnea (CSA), insomnia, or HF-related nighttime symptoms, such as paroxysmal nocturnal dyspnea or nocturia.^{28,30–32} The concept of sleep quality is multi-dimensional. The dimensions of sleep quality include the general quality of one's sleep, duration of sleep, the time required to fall asleep (sleep latency), the percent of time spent in bed asleep (sleep efficiency), disrupted sleep, and the use of sleep medication.³³ Redeker and Stein²⁶ found that patients with HF had significantly increased time spent awake after sleep onset, more disrupted sleep, and more daytime symptoms including EDS compared to people without HF. Another study by Redeker et al.³² found significant differences in the time spent awake after sleep onset and sleep efficiency with increasing severity of SRBD in HF patients. Also, participants' reports of sleep quality and EDS were no more common in those with SRBD than without, suggesting that the characteristics of disturbed sleep in HF are uniquely different than SRBD in the general population. In addition to SRBD, contributing factors to disturbed sleep may include aging, comorbidities, mental health, and medications.^{27,28,34,35}

In the general population, evidence from behavioral and physiological studies have shown that sleep is related to hippocampal function, i.e., memory consolidation.²⁴ Researchers have found that self-reported poor sleep quality is associated with reduced prefrontal cortex function, i.e., attention and executive function.^{19–21} For example, Nebes et al.¹⁹ demonstrated that global sleep quality is associated with attention, executive function, and global cognition. In this study, each dimension of sleep quality affects different domains of cognitive function. They found longer sleep latency was associated with poorer global cognitive function and executive function, and higher sleep efficiency is associated with better global cognitive function and attention.

Daytime symptoms (e.g. EDS or daytime dysfunction) of disturbed sleep and sleep disorders may be related to cognitive decline as well. Sleepiness from sleep deprivation slows responses and increases errors in attention tasks in healthy adults.²² In a population-based study of 1,026 older adults, EDS was a risk factor for reduced attention and memory.²³ In individuals with HF, it is important to evaluate EDS because it is known to affect medication adherence, an essential facet of self-care.³⁶ However, within the HF population, limited information exists on whether daytime symptoms due to disturbed sleep influence cognitive function.

Only a few researchers have explored the relationships between sleep quality and cognition in individuals with HF and their findings have been inconsistent. Garcia et al.³⁷ reported that 96% of older adults with HF experienced poor sleep quality as measured by the Pittsburgh Sleep Quality Index (PSQI) score, with a mean score of 15.23 (SD = 7.12). In this study, poor sleep quality was associated with reduced attention and executive function, but not memory.³⁷ Two other researchers examined whether specific sleep disorders were related to

cognitive function. Knecht et al.³⁸ examined 42 HF patients with SRBD and 138 HF patients without SRBD. Seventy-one percent had normal cognitive function according to the Modified Mini-Mental Status Examination. The patients with both HF and SRBD performed worse on tasks related to global cognitive function and attention as compared to HF patients without SRBD. Hjelm et al.³⁹ examined whether or not SRBD and insomnia were associated with cognitive impairment in a sample of 137 older adults with HF. Their results indicated that 78% had normal global cognitive function according to the Mini-Mental Status Examination (MMSE) scores. Their study also showed that insomnia was associated with poor scores on global cognition, but that SRBD and EDS were not. Researchers did not explore the relationship between different dimensions of sleep quality and cognitive function.

The overall purpose of this study was to examine whether self-reported sleep quality and daytime symptoms among individuals with HF are associated with selected domains of cognitive function, specifically, attention, immediate memory, and executive function. The specific aims of this study are (1) to examine how global sleep quality and dimensions of sleep quality, such as sleep duration, sleep disturbances, sleep latency, and sleep efficiency, are related to cognitive function tests of attention, immediate memory, and executive function and (2) to examine how EDS and daytime dysfunction due to sleep disturbance are related to cognitive tests of attention, immediate memory, and executive function.

Methods

Using a descriptive, cross-sectional design, we conducted a secondary analysis of data from a larger study in which researchers documented the psychometric properties of a brief, but comprehensive neuropsychological battery in HF patients.^{11,40} The original study was approved by the institutional review board.

Sample

Eighty patients with HF were recruited from a community-based, tertiary care HF clinic serving three mid-western states (Western Iowa, South Dakota, and Nebraska). Participants were age 50 or older and had a history of HF for at least six months prior to study enrollment. All participants were medically stable and had been on American Heart Association guideline-based⁴¹ medication regimens for at least four weeks. Exclusion criteria included a) any signs of cardiovascular instability including but not limited to history of a myocardial infarction, unstable angina, coronary artery bypass surgery, percutaneous transluminal coronary angioplasty, or insertion of an implantable device including pacemaker or defibrillator within three months of study enrollment; severe renal failure defined by serum creatinine > 2.5 milligrams per deciliter; or anemia, b) conditions known to affect cognitive function⁴² including a previous diagnosis of dementia or neurological disease, such as Alzheimer's disease, Parkinson's Disease, epilepsy, or stroke; a history of substance abuse or treatment for substance abuse; aspartate aminotransferase (AST) > 40 units per liter for males or AST > 72 units per liter for females, or an alkaline phosphatase (ALP) > 200 units per liter, and c) conditions that affect sleep (e.g., dysregulated sleep schedules or shift workers).

Measurements

Sleep quality—Sleep quality was measured using the PSQI. The PSQI is a self-report measure of global sleep quality. The instrument consists of 19 items that are grouped into seven subscales reflecting different dimensions of sleep, such as sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction. Each subscale was weighted equally on a 0 to 3 scale, yielding a global score from 0 to 21. Poor sleep quality is defined as a global PSQI score ≥ 5 . The measure has adequate internal consistency among adults (Cronbach's $\alpha = 0.83$).³³ We reported the raw scores for sleep duration, sleep latency, sleep efficiency, and use of sleep medications subscales because they are meaningful descriptions of different dimensions of sleep quality.

EDS—The Epworth Sleepiness Scale (ESS) is a self-report questionnaire used to identify individuals with EDS.³⁵ Participants were asked to rate their likelihood of falling asleep during eight different daily situations. The scale covers normal to pathologic sleep propensities in particular situations (e.g., social conversation, watching TV, driving a car). Scores range from 0 to 24 with scores ≥ 10 indicating significant EDS. Researchers have demonstrated good construct validity and reliability of ESS in adults (Cronbach's $\alpha = 0.88$).⁴³

Dementia screening—The MMSE was used as a screening tool for dementia. MMSE scores < 24 are considered to indicate dementia.⁴⁴ Using the standard cutoff point of 24, sensitivity and specificity are 98% and 89% respectively in older adults.⁴⁵

Cognitive Function—Cognitive function was measured using a comprehensive neuropsychological battery. The feasibility of using the neuropsychological battery has been documented elsewhere.⁴⁰ Briefly, the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) is a widely used measure of global cognitive function and five cognitive domains (immediate memory, visual/spatial construction, language, attention, and delayed memory).⁴⁶ The total scale score represents global cognitive function. The index scores from the five subscales represent different cognitive domains including variables of interest, i.e., attention and immediate memory. The RBANS has good reliability and validity and has demonstrated usefulness with HF patients.^{40,47,48} For this study, Randolph's norms were used.⁴⁶

Digit span test and coding test from RBANS were used to measure attention. The digit span test requires participants to recall an increasing series of numbers. The possible total score is from 0 to 16, with higher scores indicating greater attention. For coding, participants are given 90 seconds to match a series of symbols to numbers using a key that shows corresponding numbers and symbols. Coding assesses complex scanning, visual tracking, and processing speed.⁴⁹ The possible total score is from 0 to 89 with higher scores indicating better ability.

List learning and the story memory tests from RBANS were used to measure immediate memory. In the list learning test, ten common nouns are read in four consecutive trials. Participants are asked to remember as many words as possible in each trial. The possible total score is from 0 to 40 with higher scores indicating better immediate recall. In the story

memory test, participants are asked to recall as much of the story as possible after listening to a story once. The possible total score is from 0 to 24 with higher scores indicating better immediate memory.

Overall executive function was measured using the Trail Making Test part B (TMT-B) raw scores and the Letter Fluency test. TMT-B was used to measure complex visual scanning, attention, processing speed, and executive function. In the TMT-B, participants are asked to connect a series of dots with circled numbers and letters, alternating between numbers and letters in ascending order (e.g., 1, A, 2, B, etc.) as quickly as they can. The time taken to complete is used as the score.⁵⁰ Letter or phonemic Fluency was tested by asking participants to recall as many words as possible in one minute that begin with the letter 'D.' The Letter Fluency test requires skills of organization and recall, and involves processing speed. Thus, letter fluency is another measure of executive function, and lower scores are associated with degenerative neurologic processes.⁵¹ For descriptive purposes, all the cognitive function test scores were transformed into Z scores. A Z- score less than a -1.5 standard deviation indicates cognitive impairment.

Comorbid Conditions—The presence and severity of comorbid conditions were evaluated using the 16-item Charlson Comorbidity Index.⁵² Charts were reviewed for 12 comorbid conditions (yes/ no). The comorbidity index is calculated by using assigned weights for both the number and the severity of the comorbidities for each condition (0, 1, 3, or 6). A higher score indicates greater severity.⁵²

Depressive symptoms—Depressive symptoms were evaluated using the eight-item Patient Health Questionnaire (PHQ-8). The measure is based on the depression criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Scores range from 0 to 24 (0 to 4 = no symptoms, 5 to 9 = mild symptoms, 10 to 14 = moderate symptoms, 15 to 19 = moderately severe symptoms, and 20 to 24 =severe symptoms.)^{53,54} Cronbach's alpha in an HF sample was 0.82.⁹

Procedures—Following informed consent, participants provided demographic information, i.e., age, sex, and years of education, and completed questionnaires, i.e., PSQI, ESS, Charlson Comorbidity Index, and PHQ-8. Cognitive function tests were administered to assess multiple cognitive domains. Chart abstraction was completed to obtain clinical data including the duration of HF disease in months, left ventricular ejection fraction (LVEF), New York Heart Association (NYHA) HF classification (I, II, III, or IV),⁵⁵ a diagnosis of SRBD and whether the participant is receiving positive airway pressure treatment, the number of medications participants were taking, and the number and type of comorbid illnesses.

Statistical Analysis

Missing data and variable distributions were evaluated, and appropriately corrected prior to analyses. Descriptive statistics were performed to characterize the sample and to describe overall global sleep quality, sleep quality characteristics, and cognitive function. Multiple linear regressions were conducted to identify the relationships between sleep quality and

cognition. This included relationships between global sleep quality and cognition, i.e., attention, immediate memory, and executive function, the relationships between dimensions of sleep quality, i.e., sleep duration, sleep disturbances, sleep latency, and sleep efficiency and cognition, i.e., attention, immediate memory, and executive function, and the relationship between daytime symptoms, i.e., EDS and daytime dysfunction, and cognition, i.e., attention, immediate memory, and executive function, controlling for covariates. Cognitive scores were included as the dependent variable and sleep quality characteristic scores and covariates were included as the independent variables.

Covariates were age, sex, education, comorbidities, and LVEF, because these factors have been identified as important contributors to cognitive function in the neuropsychological literature.^{42, 56} Prior to the analyses, multicollinearity among covariates was examined using the variance inflation factor and tolerance measures and assumptions, such as normality, linearity, independence, and constant variance were verified using residual plots. Type I error rate was adjusted using the false discovery rate method.⁵⁷ The significance level for the study was $\alpha = 0.05$. All analyses were conducted using Statistical Analysis System (SAS) version 9.3 (SAS Institute Inc., Cary, North Carolina).

Results

Sample characteristics

Seventy patients completed the neuropsychological battery and other questionnaires. Two participants were excluded because they had dysregulated sleep or were shift workers. This yielded a sample of 68 adults with HF for whom we had complete questionnaires. The mean age of the sample was 72 (SD = 11) years. Participants were predominantly male (63%), and Caucasian (100%), with a mean education of 14 years (SD = 3) (Table 1). 54% of the sample had NYHA Class III HF, with a mean LVEF of 38 (SD = 11). The sample was relatively healthy with a mean Charlson comorbidity index score of 5 (SD = 2). Seven participants (10%) had a pre-existing diagnosis of SRBD and were being treated with positive airway pressure therapy. The mean PHQ-8 was 3.74 (SD = 3.84). Forty-six (67%) had no depressive symptoms, 17 (25%) had mild depressive symptoms, 3 (4%) had moderate depressive symptoms, and 2 (3 %) had moderately severe symptoms.

Sleep quality characteristics and EDS in HF

Overall, the mean score for global sleep quality was 5.04 (SD = 2.80); more than half (53%) of patients were classified as “poor sleepers,” using the PSQI global cut off score of > 5 . The subscale scores among these individuals with HF were within the normal range for community-dwelling older adults without HF. Forty-one percent of participants reported night time awakenings more than three times a week; 51 percent said they awaken during the night to use the bathroom more than three times a week. More than one third of the sample reported using sleep medications within the previous month. The average ESS score was 5.74 (SD = 3.61). Five of 68 (7 %) of participants had ESS scores greater than 10, the clinical cutoff for EDS (Table 2).

Cognitive function in HF

None of the participants had scores indicative of dementia on the MMSE, i.e., < 24 consistent with the eligibility criteria (Table 3). However, there was evidence of cognitive impairment defined by Z scores in this HF sample. Ten participants (15%) had impaired global cognitive function as indicated by their RBANS total score. Impairments included problems with immediate memory ($n=15$, 25%) and attention ($n=13$; 19%). Executive function assessed with letter fluency was most often impaired ($n = 35$; 52%), whereas, participants demonstrated less executive function impairment on the TMT-B ($n = 6$; 9%).

Relationships between sleep quality and cognitive function

No significant relationship was found between global sleep quality and cognitive function in this HF sample, after adjusting for covariates (Table 4). Global sleep quality, i.e., PSQI also did not explain the variance in scores on cognitive function, i.e., RBANS attention index, RBANS immediate memory index, letter fluency test, or TMT- B. Sleep quality characteristics, such as sleep duration, sleep disturbances, sleep latency, and sleep efficiency were not associated with cognitive function, i.e., RBANS attention index, RBANS immediate memory index, letter fluency, or TMT-B.

Relationships between daytime symptoms and cognitive function

The degree of EDS, i.e., ESS, did not explain the variance in cognitive tests, i.e., RBANS attention index, RBANS immediate memory index, letter fluency, or TMT-B, after controlling for covariates (Table 5). However, regression analysis indicated that daytime dysfunction measured by PSQI subscale was significantly related with several RBANS subscales; daytime dysfunction was significantly associated with attention ($\beta = -6.81$, $p = 0.049$, $R^2 = 0.037$, adj $R^2 = 0.023$) and with letter fluency ($\beta = -2.24$, $p = 0.01$, $R^2 = 0.077$, adj $R^2 = 0.063$). Specifically, daytime dysfunction was significantly associated with the coding test among measures of attention ($\beta = -3.96$, $p = 0.02$, $R^2 = 0.039$, adj $R^2 = 0.024$).

In regression models, higher previous years of education was significantly associated with higher scores on cognitive tests. Older age was associated with poorer scores on the cognitive tests. However, other covariates such as gender, comorbidities, and LVEF were not related to cognitive test scores.

Discussion

Half of the individuals with HF in this study reported sleep quality scores that were at the cut off for poor sleep quality. After adjusting for demographic and clinical variables, neither sleep quality nor EDS were related to any of the domains of cognitive function. However, daytime dysfunction due to poor sleep was positively related to two domains of cognitive functioning, attention and executive function.

We found that increased daytime dysfunction was significantly associated with reduced attention and executive function. More specifically, daytime dysfunction was significantly related to the lower scores on the coding test and letter fluency test; both require the ability to process information in a given amount of time. Although daytime dysfunction was not

associated with another measure of executive function that reflects processing speed, i.e., TMT-B, individuals with HF who reported greater daytime dysfunction had slower processing speeds. This study provides preliminary support for a relationship between sleep-related daytime dysfunction and prefrontal lobe processes. These findings are consistent with previous findings in the general population and HF.^{58–60} Inadequate sleep can result in wake state instability and a decreased ability to sustain one's attention and an increased duration of lapses.^{22,61} However, further investigation is needed to explore factors that influence daytime dysfunction in HF samples, and to examine the relationship between daytime dysfunction and TMT-B.

The prevalence of EDS was only 7%, unlike previously reported rates for HF populations, i.e., 21% ~ 44% of participants had scores greater than 10 on ESS.^{26,62–65} Our results are consistent with those of Taranto Montemurro et al.⁶⁶ who found an inverse relationship between EDS and sympathetic nervous system activity in HF patients. Although people with OSA in the general population report EDS, patients with HF, even those with OSA and objective daytime sleepiness, have reported similar or lower ESS scores compared to individuals without HF.^{67,68} With such a low incidence of EDS, there was no significant relationship between EDS and cognitive function. This is consistent with findings from Hjelm et al.³⁹ who did not find any association between EDS and cognitive function among individuals with HF. However, in the general population EDS is negatively related to attention and executive function.⁶⁹

Overall, our participants with HF had overall better sleep quality, indicated by PSQI mean scores around 5, than reported in prior studies. In previous HF literature, PSQI scores ranged from 7.17 ~ 9.06.^{26,27,29,31,32,64} Sleep duration, sleep efficiency, and sleep latency in this sample were similar to those described for healthy older adults without HF.^{70–72} Redeker and Stein²⁶ reported that HF patients have poorer global sleep quality and poorer results on some subscales including sleep latency, sleep disturbance, and daytime dysfunction compared to those without HF. The mean of these scores among the participants with HF in this study were similar to those found in their control group.²⁶ There are three possible explanations for better sleep quality scores in this sample. First, participants may have underreported their sleep problems and overestimated their sleep quality. Our sample is older than previous samples, and older adults in the general population often underreport their sleep problems.⁷³ In addition, older adults with chronic disease often attribute their sleep problems to age, and therefore may not recognize that they are experiencing sleep problems.⁷⁴ Second, the participants in this study had a lower rate of diagnosis of SRBD than was previously reported.⁷⁵ Participants may have undetected SRBD; we relied on chart review without objective screening. Finally, sample size was not large enough to detect variability in sleep quality, daytime symptoms, and cognition among individuals with HF.

We did not find significant relationships between self-reported global sleep quality and cognitive function. While 53% of participants fell into the 'poor sleeper' category, their global sleep scores were barely within the cutoff. In the previous research, global sleep quality scores were higher, and both sleep quality and the existence of SRBD in HF samples were associated with cognitive impairment.^{37–39} Reduced cardiac output from HF or other

comorbid conditions may have greater impact on cognitive function than sleep, but there is a need for further studies to explore the causal relationship between HF, sleep, and cognition.

This study makes several significant contributions to previous research. First, it is one of the few studies that assessed the association of self-reported sleep quality and daytime functions with cognitive function in a sample of HF patients. Second, this study is one of the first to explore relationships between multiple dimensions of sleep and cognitive function among individuals with HF; we have extended prior research by investigating aspects of sleep beyond the common sleep disorders previously examined. Third, measuring several dimensions of sleep quality, EDS, and cognitive function (neuropsychological battery) enabled us to examine sleep quality characteristics and domains of cognitive function in HF more thoroughly.

This study has several limitations. First, this is a secondary analysis of an existing dataset; therefore, the study was not powered to answer our primary aim. Second, the small sample size limits the generalizability of the findings. Third, while depression and other factors have been shown to affect cognitive function, the low prevalence of depression in our sample did not allow for exploring such a relationship. Fourth, self-reported measures were used; it is unclear whether objective measures such as polysomnography would have provided more specific sleep quality data in this small sample. Finally, the design of this study was cross-sectional, so causality cannot be established. Despite these limitations, this study is one of the first to report the relationships among multiple aspects of sleep and cognition in individuals with HF.

Future studies will be needed to better establish the relationship between sleep and cognitive function, especially cognitive domains of attention and executive function. Samples from larger and more diverse groups will be required to increase the generalizability of the results. More objective measures of sleep, such as in-lab overnight sleep studies to evaluate objective sleep quality and rule out sleep disorders known to affect cognition or actigraphy studies to evaluate sleep wake pattern would augment the information provided from self-reported questionnaires. Electroencephalography would provide more in-depth information about cortical activity during sleep.⁷⁶ Further, longitudinal studies would increase researchers' understanding of the trajectory and causality of sleep and cognitive changes among individuals with HF. Finally, changes in brain structure and perfusion precede cognitive changes by months to years.⁷⁷ Adding high resolution brain MRI to such studies could help illuminate potential mechanisms linking daytime dysfunction and sleep.

Despite the limitations of this study, our results have implications for practice. HF patients with a higher degree of daytime dysfunction demonstrate reduced ability to process information quickly. Health care providers need to be aware that processing speed may be impaired in such individuals and work to provide slow, clear, and concise instructions related to medication or self-care particularly during rushed periods such as at discharge or during clinic visits. Written instructions and involvement of family members may be vitally important during hurried or otherwise brief guidance periods to reduce readmissions. Health care professionals also need to be mindful of factors contributing to daytime dysfunction and intervene to limit the impact of daytime dysfunction on cognitive function.

In conclusion, this study demonstrates more variability in sleep quality among individuals with HF than has been reported in the past. In this sample, the majority of our subjects did not report significant problems with sleep quality, and hence the relationship between disturbed sleep and cognition could not be adequately tested. Daytime dysfunction related to sleep was significantly related to cognitive function in areas related to attention and executive function. Given the self-management challenges of individuals with HF, we believe that replication of this research is needed using a prospective design, using larger samples, objective sleep measures, and high-resolution brain MRI.

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References

1. Giamouzis G, Kalogeropoulos A, Georgiopoulos V, et al. Hospitalization epidemic in patients with heart failure: risk factors, risk prediction, knowledge gaps, and future directions. *J Card Fail.* 2011; 17(1):54–75. [PubMed: 21187265]
2. Calvert MJ, Freemantle N, Cleland JGF. The impact of chronic heart failure on health-related quality of life data acquired in the baseline phase of the CARE-HF study. *Eur J Heart Fail.* 2005; 7(2):243–251. [PubMed: 15701474]
3. Hunt SA, Abraham WT, Chin MH, et al. 2009 Focused Update Incorporated Into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines Developed in Collaboration With the International Society for Heart and Lung Transplantation. *J Am Coll Cardiol.* 2009; 53(15):e1–e90. [PubMed: 19358937]
4. Baker DW, Einstadter D, Thomas C, Cebul RD. Mortality trends for 23,505 Medicare patients hospitalized with heart failure in Northeast Ohio, 1991 to 1997. *Am Heart J.* 2003; 146(2):258–264. [PubMed: 12891193]
5. Chaudhry SI, Wang Y, Gill TM, Krumholz HM. Geriatric conditions and subsequent mortality in older patients with heart failure. *J Am Coll Cardiol.* 2010; 55(4):309–316. [PubMed: 20117435]
6. Lee DS, Austin PC, Rouleau JL, Liu PP, Naimark D, Tu JV. Predicting mortality among patients hospitalized for heart failure: derivation and validation of a clinical model. *JAMA J Am Med Assoc.* 2003; 290(19):2581–2587.
7. Vogels RLC, Scheltens P, Schroeder-Tanka JM, Weinstein HC. Cognitive impairment in heart failure: a systematic review of the literature. *Eur J Heart Fail.* 2007; 9(5):440–449. [PubMed: 17174152]
8. Pressler SJ. Cognitive functioning and chronic heart failure: a review of the literature (2002–July 2007). *J Cardiovasc Nurs.* 2008; 23(3):239–249. [PubMed: 18437066]
9. Pressler SJ, Subramanian U, Kareken D, et al. Cognitive deficits in chronic heart failure. *Nurs Res.* 2010; 59(2):127–139. [PubMed: 20216015]
10. Bennett SJ, Sauvé MJ. Cognitive deficits in patients with heart failure: a review of the literature. *J Cardiovasc Nurs.* 2003; 18(3):219–242. [PubMed: 12837012]
11. Bauer L, Pozehl B. Measurement of cognitive function in chronic heart failure: a feasibility study. *Appl Nurs Res.* 2011; 24(4):223–228. [PubMed: 20974084]

12. Woo MA, Kumar R, Macey PM, Fonarow GC, Harper RM. Brain injury in autonomic, emotional, and cognitive regulatory areas in patients with heart failure. *J Card Fail.* 2009; 15(3):214–223. [PubMed: 19327623]
13. Vogels RLC, Oosterman JM, van Harten B, et al. Neuroimaging and correlates of cognitive function among patients with heart failure. *Dement Geriatr Cogn Disord.* 2007; 24(6):418–423. [PubMed: 17938570]
14. Pan A, Kumar R, Macey PM, Fonarow GC, Harper RM, Woo MA. Visual assessment of brain magnetic resonance imaging detects injury to cognitive regulatory sites in patients with heart failure. *J Card Fail.* 2013; 19(2):94–100. [PubMed: 23384634]
15. Kumar R, Woo MA, Macey PM, Fonarow GC, Hamilton MA, Harper RM. Brain axonal and myelin evaluation in heart failure. *J Neurol Sci.* 2011; 307(1–2):106–113. [PubMed: 21612797]
16. Woo MA, Macey PM, Fonarow GC, Hamilton MA, Harper RM. Regional brain gray matter loss in heart failure. *J Appl Physiol Bethesda Md* 1985. 2003; 95(2):677–684.
17. Bauer L, Johnson JK, Pozehl BJ. Cognition in heart failure: An overview of the concepts and their measures. *J Am Acad Nurse Pract.* 2011; 23(11):577–585. [PubMed: 22023229]
18. Bennett SJ, Sauvé MJ, Shaw RM. A conceptual model of cognitive deficits in chronic heart failure. *J Nurs Scholarsh Off Publ Sigma Theta Tau Int Honor Soc Nurs Sigma Theta Tau.* 2005; 37(3): 222–228.
19. Nebes RD, Buysse DJ, Halligan EM, Houck PR, Monk TH. Self-reported sleep quality predicts poor cognitive performance in healthy older adults. *J Gerontol B Psychol Sci Soc Sci.* 2009; 64B(2):180–187. [PubMed: 19204069]
20. Blackwell T, Yaffe K, Ancoli-Israel S, et al. Association of sleep characteristics and cognition in older community-dwelling men: the MrOS sleep study. *Sleep.* 2011; 34(10):1347–1356. [PubMed: 21966066]
21. Benitez A, Gunstad J. Poor sleep quality diminishes cognitive functioning independent of depression and anxiety in healthy young adults. *Clin Neuropsychol.* 2012; 26(2):214–223. doi: 10.1080/13854046.2012.658439. [PubMed: 22335237]
22. Lim J, Dinges DF. Sleep Deprivation and Vigilant Attention. *Ann N Y Acad Sci.* 2008; 1129(1): 305–322. [PubMed: 18591490]
23. Ohayon MM, Vecchierini M. Daytime sleepiness and cognitive impairment in the elderly population. *Arch Intern Med.* 2002; 162(2):201–208. [PubMed: 11802754]
24. Walker MP, Stickgold R. Sleep-dependent learning and memory consolidation. *Neuron.* 2004; 44(1):121–133. [PubMed: 15450165]
25. Jaarsma T, Halfens R, Abu-Saad HH, Dracup K, Stappers J, van Ree J. Quality of life in older patients with systolic and diastolic heart failure. *Eur J Heart Fail.* 1999; 1(2):151–160. [PubMed: 10937925]
26. Redeker NS, Stein S. Characteristics of sleep in patients with stable heart failure versus a comparison group. *Heart Lung J Crit Care.* 2006; 35(4):252–261.
27. Erickson VS, Westlake CA, Dracup KA, Woo MA, Hage A. Sleep disturbance symptoms in patients with heart failure. *AACN Clin Issues.* 2003; 14(4):477–487. [PubMed: 14595207]
28. Broström A, Johansson P. Sleep disturbances in patients with chronic heart failure and their holistic consequences-what different care actions can be implemented? *Eur J Cardiovasc Nurs J Work Group Cardiovasc Nurs Eur Soc Cardiol.* 2005; 4(3):183–197.
29. Chen HM, Clark AP, Tsai LM, Chao YFC. Self-reported sleep disturbance of patients with heart failure in Taiwan. *Nurs Res.* 2009; 58(1):63–71. [PubMed: 19092556]
30. Riegel B, Weaver TE. Poor Sleep and Impaired Self-Care: Towards a Comprehensive Model Linking Sleep, Cognition, and Heart Failure Outcomes. *Eur J Cardiovasc Nurs J Work Group Cardiovasc Nurs Eur Soc Cardiol.* 2009; 8(5):337–344.
31. Riegel B, Glaser D, Richards K, et al. Modifiable factors associated with sleep dysfunction in adults with heart failure. *Eur J Cardiovasc Nurs J Work Group Cardiovasc Nurs Eur Soc Cardiol.* 2011
32. Redeker NS, Muench U, Zucker MJ, et al. Sleep disordered breathing, daytime symptoms, and functional performance in stable heart failure. *Sleep.* 2010; 33(4):551–560. [PubMed: 20394325]

33. Buysse DJ, Reynolds CF III, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh sleep quality index: A new instrument for psychiatric practice and research. *Psychiatry Res.* 1989; 28(2):193–213. [PubMed: 2748771]
34. Ancoli-Israel S, Cooke JR. Prevalence and comorbidity of insomnia and effect on functioning in elderly populations. *J Am Geriatr Soc.* 2005; 53(7 Suppl):S264–S271. [PubMed: 15982375]
35. Redeker NS. Sleep disturbance in people with heart failure: implications for self-care. *J Cardiovasc Nurs.* 2008; 23(3):231–238. [PubMed: 18437065]
36. Riegel B, Moelter ST, Ratcliffe SJ, et al. Excessive daytime sleepiness is associated with poor medication adherence in adults with heart failure. *J Card Fail.* 2011; 17(4):340–348. [PubMed: 21440873]
37. Garcia S, Alosco ML, Spitznagel MB, et al. Poor sleep quality and reduced cognitive function in persons with heart failure. *Int J Cardiol.* 2012; 156(2):248–249. [PubMed: 22360947]
38. Knecht KM, Alosco ML, Spitznagel MB, et al. Sleep apnea and cognitive function in heart failure. *Cardiovasc Psychiatry Neurol.* 2012; 2012:402079. [PubMed: 22745901]
39. Hjelm C, Strömberg A, Arestedt K, Broström A. Association between sleep-disordered breathing, sleep-wake pattern, and cognitive impairment among patients with chronic heart failure. *Eur J Heart Fail.* 2013; 15(5):496–504. [PubMed: 23392278]
40. Bauer L, Pozehl B, Hertzog M, Johnson J, Zimmerman L, Filipi M. A brief neuropsychological battery for use in the chronic heart failure population. *Eur J Cardiovasc Nurs J Work Group Cardiovasc Nurs Eur Soc Cardiol.* 2012; 11(2):223–230.
41. Roger VL, Go AS, Lloyd-Jones DM, et al. Heart Disease and Stroke Statistics—2012 Update A Report From the American Heart Association. *Circulation.* 2012; 125(1):e2–e220. [PubMed: 22179539]
42. Lezak, MD.; Howieson, D.; Bigler, ED.; Tranel, D. *Neuropsychological Assessment.* Oxford; New York: Oxford University Press; 2012.
43. Johns MW. Daytime sleepiness, snoring, and obstructive sleep apnea. The Epworth Sleepiness Scale. *CHEST J.* 1993; 103(1):30–36.
44. Folstein MF, Folstein SE, McHugh PR. “Mini-mental state”: A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res.* 1975; 12(3):189–198. [PubMed: 1202204]
45. O'Connor DW, Pollitt PA, Hyde JB, et al. The reliability and validity of the Mini-Mental State in a British community survey. *J Psychiatr Res.* 1989; 23(1):87–96. [PubMed: 2666647]
46. Randolph C, Tierney MC, Mohr E, Chase TN. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): Preliminary Clinical Validity. *J Clin Exp Neuropsychol.* 1998; 20(3):310–319. [PubMed: 9845158]
47. Hoth KF, Poppas A, Moser DJ, Paul RH, Cohen RA. Cardiac dysfunction and cognition in older adults with heart failure. *Cogn Behav Neurol Off J Soc Behav Cogn Neurol.* 2008; 21(2):65–72.
48. Wolfe R, Worrall-Carter L, Foister K, Keks N, Howe V. Assessment of cognitive function in heart failure patients. *Eur J Cardiovasc Nurs J Work Group Cardiovasc Nurs Eur Soc Cardiol.* 2006; 5(2):158–164.
49. Schear JM, Sato SD. Effects of visual acuity and visual motor speed and dexterity on cognitive test performance. *Arch Clin Neuropsychol.* 1989; 4(1):25–32. [PubMed: 14589551]
50. Reitan, RM. *The Halstead-Reitan Neuropsychological Test Battery: Theory and Clinical Interpretation.* Tucson, Ariz: Neuropsychology Press; 1985.
51. Kramer JH, Jurik J, Sha SJ, et al. Distinctive neuropsychological patterns in frontotemporal dementia, semantic dementia, and Alzheimer disease. *Cogn Behav Neurol Dec* 2003. 2003; 16(4): 211–218.
52. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis.* 1987; 40(5):373–383. [PubMed: 3558716]
53. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med.* 2001; 16(9):606–613. [PubMed: 11556941]
54. Kroenke K, Spitzer RL. The PHQ-9: A new depression diagnostic and severity measure. *Psychiatr Ann.* 2002; 32(9):509–515.

55. Dolgin, M., editor. New York Heart Association Criteria Committee. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th ed.. Boston: Little, Brown; 1994.
56. Heckman GA, Patterson CJ, Demers C, St Onge J, Turpie ID, McKelvie RS. Heart failure and cognitive impairment: challenges and opportunities. *Clin Interv Aging*. 2007; 2(2):209–218. [PubMed: 18044137]
57. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J R Stat Soc Ser B Methodol*. 1995; 57(1):289–300.
58. Jones K, Harrison Y. Frontal lobe function, sleep loss and fragmented sleep. *Sleep Med Rev*. 2001; 5(6):463–475. [PubMed: 12531154]
59. Vartanian O, Bouak F, Caldwell JL, et al. The effects of a single night of sleep deprivation on fluency and prefrontal cortex function during divergent thinking. *Front Hum Neurosci*. 2014; 8
60. Drummond SP, Brown GG, Gillin JC, Stricker JL, Wong EC, Buxton RB. Altered brain response to verbal learning following sleep deprivation. *Nature*. 2000; 403(6770):655–657. [PubMed: 10688201]
61. Dinges DF, Pack F, Williams K, et al. Cumulative sleepiness, mood disturbance, and psychomotor vigilance performance decrements during a week of sleep restricted to 4–5 hours per night. *Sleep*. 1997; 20(4):267–277. [PubMed: 9231952]
62. Chen H-M, Clark AP, Tsai L-M, Liu Y, Wu L-M, Wu S-J. Excessive Daytime Sleepiness in Taiwanese People With Heart Failure. *J Nurs Res March* 2013. 2013; 21(1):39–48.
63. Riegel B, Ratcliffe SJ, Sayers SL, et al. Determinants of excessive daytime sleepiness and fatigue in adults with heart failure. *Clin Nurs Res*. 2012; 21(3):271–293. [PubMed: 21878581]
64. Broström A, Strömberg A, Dahlström U, Fridlund B. Sleep difficulties, daytime sleepiness, and health-related quality of life in patients with chronic heart failure. *J Cardiovasc Nurs*. 2004; 19(4): 234–242. [PubMed: 15326979]
65. Johansson P, Arestedt K, Alehagen U, Svanborg E, Dahlström U, Broström A. Sleep disordered breathing, insomnia, and health related quality of life -- a comparison between age and gender matched elderly with heart failure or without cardiovascular disease. *Eur J Cardiovasc Nurs J Work Group Cardiovasc Nurs Eur Soc Cardiol*. 2010; 9(2):108–117.
66. Taranto Montemurro L, Floras JS, Millar PJ, et al. Inverse relationship of subjective daytime sleepiness to sympathetic activity in patients with heart failure and obstructive sleep apnea sleepiness and sympathetic activity. *CHEST J*. 2012; 142(5):1222–1228.
67. Hastings PC, Vazir A, O'Driscoll DM, Morrell MJ, Simonds AK. Symptom burden of sleep-disordered breathing in mild-to-moderate congestive heart failure patients. *Eur Respir J Off J Eur Soc Clin Respir Physiol*. 2006; 27(4):748–755.
68. Arzt M, Young T, Finn L, et al. Sleepiness and sleep in patients with both systolic heart failure and obstructive sleep apnea. *Arch Intern Med*. 2006; 166(16):1716–1722. [PubMed: 16983049]
69. Jackson ML, Howard ME, Barnes M. Cognition and daytime functioning in sleep-related breathing disorders. *Prog Brain Res*. 2011; 190:53–68. [PubMed: 21531244]
70. Ohayon MM, Carskadon MA, Guilleminault C, Vitiello MV. Meta-analysis of quantitative sleep parameters from childhood to old age in healthy individuals: developing normative sleep values across the human lifespan. *Sleep*. 2004; 27(7):1255–1273. [PubMed: 15586779]
71. Ohayon MM, Vecchierini M-F. Normative sleep data, cognitive function and daily living activities in older adults in the community. *Sleep*. 2005; 28(8):981–989. [PubMed: 16218081]
72. Ancoli-Israel S. Sleep and its disorders in aging populations. *Sleep Med*. 2009; 10(Supplement 1):S7–S11. [PubMed: 19647483]
73. Lund HG, Rybarczyk BD, Perrin PB, Leszczyszyn D, Stepanski E. The Discrepancy between Subjective and Objective Measures of Sleep in Older Adults Receiving CBT for Comorbid Insomnia. *J Clin Psychol*. 2012 n/a - n/a.
74. Zilli I, Ficca G, Salzarulo P. Factors involved in sleep satisfaction in the elderly. *Sleep Med*. 2009; 10(2):233–239. [PubMed: 18387848]
75. Kasai T, Bradley TD. Obstructive Sleep Apnea and Heart Failure: Pathophysiologic and Therapeutic Implications. *J Am Coll Cardiol*. 2011; 57(2):119–127. [PubMed: 21211682]
76. Nunez, PL. *Electric Fields of the Brain: The Neurophysics of EEG*, 2nd Edition. 2 edition. Oxford ; New York: Oxford University Press; 2005.

77. Smith CD, Chebrolu H, Wekstein DR, et al. Brain structural alterations before mild cognitive impairment. *Neurol* April 17 2007. 2007; 68(16):1268–1273.

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Table 1

Demographic and clinical characteristics of the sample (N=68).

	Mean $\pm$ SD
	n (%)
Age (years)	72.32 $\pm$ 11.39
Male	43 (63)
Caucasian	68 (100)
Previous education (years)	13.75 $\pm$ 2.81
LVEF (%)	37.72 $\pm$ 10.94
NYHA class	
I	2 (2.9)
II	29 (42.6)
III	37 (54.4)
Disease duration	
<1y	7 (10.61)
1–5y	25 (36.76)
>5y	36 (52.94)
Heart failure etiology	
Systolic	39 (57.4)
Diastolic	29 (42.6)
Sleep-related breathing disorders	7 (10.30)
Number of comorbidities	4.2 $\pm$ 2.22
Charlson comorbidity index	5.44 $\pm$ 2.35
Number of medications	10.56 $\pm$ 3.50
PHQ-8	3.74 $\pm$ 3.84

Abbreviations: SD = standard deviation, LVEF = left ventricular ejection fraction, NYHA = New York Heart Association, PHQ-8=8-item Patient Health Questionnaire

Table 2

Sleep quality characteristics, daytime dysfunction, and daytime sleepiness of the sample (N = 68).

	Scaled scores	Raw scores
	Mean $\pm$ SD or n (%)	
Global sleep quality score (PSQI)	5.04 $\pm$ 2.80	
Subjective sleep quality	0.93 $\pm$ 0.61	0.93 $\pm$ 0.61
Sleep duration	0.65 $\pm$ 0.94	6.99 $\pm$ 1.56 hours
Sleep latency	1.01 $\pm$ 0.80	15.91 $\pm$ 14.81 minutes
Sleep efficiency	0.72 $\pm$ 0.99	86.29 $\pm$ 17.32%
Sleep disturbance	1.19 $\pm$ 0.94	6.37 $\pm$ 3.57
Use of sleep medication, n (%)	0.76 $\pm$ 1.22	21 (30.88%)
Daytime dysfunction	0.47 $\pm$ 0.70	0.68 $\pm$ 1.11
Daytime sleepiness (ESS)	5.74 $\pm$ 3.61	
Excessive daytime sleepiness ESS > 10 n (%)	5 (7.35%)	

Note: The raw scores of the PSQI seven subscales are weighted equally on a scale of 0 to 3.

Abbreviations: SD = standard deviation, ESS = Epworth Sleepiness Scale, PSQI = Pittsburgh Sleep Quality Index. Both weighted scores and raw scores of the PSQI are presented.

Table 3

Cognitive function scores of the sample (N = 68)

	Mean $\pm$ SD
MMSE (raw scores)	28.10 $\pm$ 1.83
RBANS total score (Z score)	-0.56 $\pm$ 0.92
Attention index	-0.62 $\pm$ 1.22
Immediate memory index	0.80 $\pm$ 1.06
Delayed memory index	-0.38 $\pm$ 1.01
Letter fluency ("D" words in 1-min, z-score)	-1.29 $\pm$ 1.11
TMT-B (Z score)	-0.08 $\pm$ 1.10

Abbreviations: MMSE = Mini-Mental State Examination, RBANS = Repeatable Battery for the Assessment of Neuropsychological Status, TMT-B = Trail Making Test part B

Table 4

Summary of regression analysis for sleep variables predicting neuropsychological function after adjusting for covariates[†] (N=68)

	Neuropsychological function index scores, β (95% CI)			
	Attention	Immediate memory	Executive function	
	RBANS Attention Index	RBANS Immediate Memory Index	Letter fluency	TMT-B
Global Sleep Quality	-0.49 (-1.78~0.81)	0.29 (-0.97~1.55)	0.18 (-0.51~0.16)	-0.32 (-5.06~4.42)
Sleep quality Characteristics				
Sleep latency	-0.46 (-5.79~ 4.86)	0.06 (-5.09~ 5.22)	-0.99 (-2.36~0.39)	-7.10 (-26.54~12.35)
Sleep duration	-0.69 (-5.41~ 4.02)	1.70 (-2.85~ 6.24)	0.33 (-0.90~1.57)	1.21 (-15.82~18.25)
Sleep efficiency	1.31 (-3.03~ 5.66)	0.58 (-3.64~ 4.79)	0.12 (-1.02~1.26)	4.34 (-11.35~20.03)
Sleep disturbance	-3.20 (-12.88~ 6.47)	2.57 (-6.80~ 11.93)	-0.43 (-2.97~2.11)	8.74 (-26.26~43.74)

Abbreviations: PSQI = Pittsburgh Sleep Quality Index, RBANS = Repeatable Battery for the Assessment of Neuropsychological Status, MMSE = Mini-Mental State Examination, TMT-A= Trail Making Test part A, TMT-B = Trail Making Test part B

[†] Covariates = age, gender, education, comorbidities, and left ventricular ejection fraction

*
p-value < .05

Table 5

Summary of regression analysis for daytime symptom variables predicting neuropsychological function after adjusting for covariates[†] (N=68)

	Neuropsychological function index scores, β (95% CI)			
	Attention	Immediate memory	Executive function	
	RBANS Attention Index	RBANS Immediate Memory Index	Letter fluency	TMT-B
ESS	-0.48 (-1.63 ~ 0.68)	0.33 (-0.80 ~ 1.45)	0.06 (-0.24 ~ 0.37)	-2.65 (-6.80~1.49)
Daytime dysfunction (PSQI subscale)	-6.81 (-12.57~ -1.05) *	-3.09 (-8.86~ 2.68)	-2.24 (-3.71~ -0.77) *	7.88 (-13.81~29.56)

Abbreviations: ESS =Epworth Sleepiness Scale, PSQI = Pittsburgh Sleep Quality Index, RBANS = Repeatable Battery for the Assessment of Neuropsychological Status, TMT-B = Trail Making Test part B

[†] Covariates = age, gender, education, comorbidities, and left ventricular ejection fraction

* p-value < .05