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Heart Failure Symptom Clusters and Functional Status

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Heart Failure Symptom Clusters and Functional Status

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Virginia Commonwealth University

by

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Acknowledgment

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Clinical assessment of heart failure includes symptom identification and the evaluation of the relationship of symptoms to functional status. Symptom clusters are groups of at least 2 or 3 co-occurring symptoms that are related but are independent of other groups of symptoms.

The objectives of this study are to: (1) examine relationships among symptoms commonly experienced by individuals with heart failure, (2) identify symptoms that form clusters, and (3) evaluate the impact of heart failure symptom clusters on attributes of functional status: limitations and mobility

The Theory of Unpleasant Symptoms guided the conduct of this study. Heart failure symptoms and the outcome variables functional limitations and mobility were evaluated in a convenience sample of individuals (n = 117) with a confirmed diagnosis of heart failure recruited
from an academic medical center. Principle components analysis was used to extract symptom clusters and regression analysis was used to evaluate the relationship between the symptom clusters, their interaction terms, the demographic variables, age and co-morbidity, and functional status.

Three symptom clusters, sickness behavior, discomforts of illness, and GI distress were extracted. Predictors of functional limitations ($F = 35.96, p = 0.0005, R^2 = 0.578$) included sickness behavior ($\beta = -0.681, p = 0.0005$), discomforts of illness ($\beta = -0.765, p = 0.0005$) and the interaction term between these two symptom clusters ($\beta = 0.649, p = 0.014$). This model predicted 59% of the variance in functional limitations. Predictors of limited mobility ($F = 20.68, p = 0.0005, R^2 = 0.275$) included sickness behavior ($\beta = -0.441, p = 0.0005$) and co-morbidity ($\beta = -0.200, p = 0.019$). This model predicted 28% of the variance in mobility.

Relationship between clusters of heart failure symptoms and functional limitations or mobility was observed. The interaction between discomforts of illness and sickness behaviors implies that not only do functional limitations increase as discomforts of illness increase, but increases at a faster rate when sickness behaviors are increased. Changes in sickness behaviors has the potential to improve mobility from being bed or chair bound everyday or most days to being bed or chair bound only some days.
Heart Failure Symptom Clusters: A Systematic Review

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1 Table
1 Figure
Abstract

Background: Heart failure is a prevalent chronic health condition in the United States. Individuals who have heart failure experience as many as 2 to 9 symptoms. Symptom clusters are groups of 2 to 3 symptoms that co-occur in a relationship with each other.

Objective: The purpose of this systematic review is to examine which heart failure symptoms are related and to examine heart failure symptom relationships using different symptom measurement instruments.

Methods: The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed in the conduct of this systematic review. Pub Med, Psych Info, Cumulative Index of Nursing and Allied Health Literature (CINAHL) and the Cochrane Database were searched using the search terms heart failure and a pair of symptoms.

Results: Thirty-four studies out of a total of 1316 studies identified from database searches are included in this systematic review. A moderate level of correlation was found by more than one investigator between depression and fatigue, depression and anxiety, depression and sleep, depression and pain, anxiety and fatigue, and dyspnea and fatigue. Dyspnea was included in a symptom cluster identified by 6 studies. Three investigators identified a symptom cluster composed of psychosocial or emotional symptoms.

Conclusions: The findings of this systematic review provide support for the presence of heart failure symptom clusters. Some symptom relationships such as the relationships between fatigue and anxiety or sleep or pain were dependent on the symptom characteristics studied. Instrument selection affected the persistence of relationships among heart failure symptoms.
These finding suggest that studies defining the phenotype of individual heart failure symptoms may be a beneficial step in the study of heart failure symptom clusters.
Background

Heart failure is a clinical syndrome that affects 5.7 million adults age 20 and older. The incidence of heart failure is approximately 10 per 1000 population after 65 years of age. Heart failure is the primary diagnosis for 41.6% of visits to primary care offices and 21% of hospital emergency department visits. Symptoms, subjective reports of abnormal physical, emotional, or cognitive conditions, trigger an individual to enter the healthcare system. Dyspnea and fatigue are frequently reported symptoms by individuals seeking emergency care for heart failure and in patients followed in cardiology clinics. A growing public health concern, heart failure is a progressive and symptomatic illness with published reports suggesting that, on average, patients with heart failure experience anywhere from 2 to 9 symptoms.

Symptom clusters are groups of symptoms that co-occur, are related, and yet, are independent of other groups of symptoms. Symptom clusters are composed of at least 2 or 3 symptoms. Although their recognition and use in the diagnosis and treatment of disease is not new, symptom cluster research is considered a new frontier in the study of symptoms. Attributes of a symptom cluster include common etiology, concurrence, relationship, and stability. Heart failure, for example, provides a common etiology for symptoms such as dyspnea, fatigue, and edema which occur together in an individual who has heart failure. Relationship is an attribute that denotes the co-occurrence of symptoms, correlation between symptoms, and shared or overlapping variance. Stability is the reliability of the symptom cluster across subjects and over time.

The purpose of this systematic review is to summarize what is known about heart failure symptoms, a step in the identification of heart failure symptom clusters. Specific aims include examining which symptoms are related and examining heart failure symptom relationships using
different symptom measurement instruments. In the context of this review, a symptom cluster will be considered to be two or more symptoms occurring together and that are related to each other. A relationship among symptoms is indicated by a statistical association.

**Methods**

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, which outline a methodology for performing systematic reviews in health care, were followed in the conduct of this systematic review. Pub Med, Psych Info, Cumulative Index of Nursing and Allied Health Literature (CINAHL) and the Cochrane Database were searched for relevant articles. Search terms were heart failure in combination with a pair of symptoms. Specific symptoms used in the literature searches were dyspnea, fatigue, anxiety, depression, edema, pain, loss of appetite, sleep disturbance, and cognitive impairment. Dyspnea, fatigue, anxiety, depression, edema, pain, loss of appetite, sleep disturbance and cognitive impairment were selected as the focal point of this review because of their prevalence and distressing nature in heart failure patients. Reported to be associated with loss of gray matter volume assessed by MRI, Sloan and Pressler observed that individuals with heart failure relate awareness of heart failure-related cognitive impairments such as difficulty with memory and concentration.

Studies were included in the review if they were published in the English language between 2000 and 2010 and reported a statistically significant relationship among 2 or more heart failure symptoms occurring together in subjects 18 years of age and older. A total of 1316 studies were identified from database and ancestry searches. Studies were excluded because they included conditions in addition to heart failure, evaluated the efficacy of an intervention for the treatment of heart failure or did not examine relationships among individual heart failure symptoms.
Seventy-nine studies were screened. Thirty-four studies meeting the inclusion criteria were included in this systematic review. Search and screening results are reported in Figure 1.

The methodological quality of the studies was evaluated using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) criteria. The STROBE criteria consist of 22 items that should be included in descriptive observational studies and in studies investigating associations between exposures and health outcomes. The specific criteria refer to the title and abstract, introduction, methods, reporting of the results, and discussion sections of the report and to the reporting of study funding. A score of 1 was given for each of the criteria on the checklist that was present in the study report. Possible methodological quality scores range from 0 to 22. A score of 22 indicates a high level of clarity and reporting of the details about the conduct of the study. Studies included in this systematic review and the scientific quality score assigned using the STROBE criteria may be found in Table 1. Scientific quality scores for the studies included in this systematic review ranged from a low score of 14 to a high score of 22. The median quality score was 18.

**Data Synthesis**

A total of 34 studies were included in the systematic review. Relationship and stability are symptom cluster attributes considered in this analysis of heart failure symptom associations. Miaskowski, Aouizerat, Dodd, and Cooper advise that before a group of symptoms can be classified as a symptom cluster, illustration of a relationship among the symptoms is required. Kim et al. characterizes the nature of symptom relationships as an associative rather than a causal connection.

Stability refers to the replicability of a symptom cluster at different times and in different samples. Stability may be assumed in symptom clusters that are established for diagnostic
purposes. In identifying stable symptom clusters Miaskowski, Dodd, and Lee suggest evaluations of symptom clusters should focus on heterogeneous patient populations to permit comparisons across patients with respect to prevalence, severity, and the effect of the symptom cluster on patient outcomes. If a symptom cluster does not occur across different patient groups the data may reflect a different underlying mechanism.

**Relationship**

Clinically, symptom clusters may be identified using observed relationships and concurrence. On the other hand symptom clusters may be identified using mathematical procedures. Barsevick suggests mathematical procedures such as bivariate correlation, factor analysis, or cluster analysis may be useful in examining symptom relationships. Investigators also used regression analysis to uncover symptom relationships in the studies included in this systematic review.

The relationship between depression and fatigue was frequently studied by investigators. Chen et al., Evangelista, et al., Fink, et al., Redeker, Sullivan, et al., and Tang, et al. reported relationships between depression and general measures of fatigue such as the Multidimensional Assessment of Fatigue Scale, the Fatigue Symptom Inventory, or the Profile of Mood States Fatigue Scale ($r = 0.34 – 0.77, p< 0.001 – 0.01$). Smith et al. observed relationships between depression and general fatigue ($r = 0.42, p < 0.001$) and depression and exertion fatigue ($r = 0.33, p < 0.001$). Falk, et al. reported relationships between depression and general fatigue ($R^2 = .145 F 21.2; \beta = .30 p < .01$), depression and reduced activity ($R^2 = .178; F=23.0; \beta = .37; p<.001$), and depression with reduced motivation ($R^2 = .110; F 13.7; \beta = .40; p<.001$). However Falk, et al. did not observe a statistically significant relationship between depression and physical fatigue or between depression and mental fatigue.
The relationship between depression and anxiety ($r = 0.52 - 0.74$, $p = 0.01 - 0.001$) persists across studies and irrespective of the instrument used to measure these symptoms. Goebel, et al.\textsuperscript{6} observed a relationship between depression and pain ($r = 0.32$, $p = 0.002$). Sullivan et al.\textsuperscript{24} found depression was related to chest pain ($r = 0.38$ to $0.43$, $p < .001$) and inversely related to bodily pain ($r = -0.37$ to $-0.47$, $p < .001$). Depression was related to the sleep characteristics, difficulty initiating and maintaining sleep ($OR = 5.09$ 95% CI 2.41 - 10.75), sleep quality ($r = 0.40 - 0.71$, $p = 0.001$), and sleep disordered breathing ($r = 0.88$, $p = 0.001$) but not to severity of sleep disordered breathing.\textsuperscript{36} Depression was also reported to be related to appetite loss ($OR = 2.28$, $p = 0.001$) and to vitality ($r = -0.40$ to $-0.44$, $p < 0.001$).\textsuperscript{24}

Relationships between fatigue and anxiety, sleep, or pain were contingent on particular characteristics of fatigue. Anxiety was related to general measures of fatigue ($r = 0.42 - 0.49$, $p < 0.001$) and to mental fatigue ($R^2=0.254$; $F =36.2$; $\beta =.39$; $p<.001$).\textsuperscript{27} Yu et al.\textsuperscript{38} detected a relationship between fatigue and the construct of anxiety/depression assessed using the Hospital Anxiety and Depression Scale (HADS) ($r = -0.50$, $p < 0.001$). Anxiety was not related to general fatigue, physical fatigue, reduced activity or reduced motivation.\textsuperscript{27} Falk, Patel, et al.\textsuperscript{27} observed that general fatigue ($\beta =0.22$; $p < 0.05$) and physical fatigue ($\beta= 0.22$, $p < 0.05$) were related to pain distress. Smith et al.\textsuperscript{26} found a relationship between cardiac pain and general fatigue ($r = 0.44$ $p < 0.001$) as well as cardiac pain and exertion fatigue ($r = 0.42$ $p < 0.001$). Difficulty with sleep was not related to fatigue intensity ($r = 0.20$, $p>.05$),\textsuperscript{39} but was related to general fatigue ($r = 0.42$, $p < .001$) and to exertion fatigue ($r = 0.29$, $p = .001$).\textsuperscript{26} Redeker et al.\textsuperscript{36} noted a non-significant relationship between global fatigue and severity of sleep disordered breathing. Stephen\textsuperscript{39} observed a relationship between fatigue intensity and nocturia ($r = 0.36$, $p < 0.01$). Falk et al.\textsuperscript{27} reported that physical fatigue was related to appetite ($\beta = 0.26$; $p<0.01$)
while nausea was related to general fatigue ($\beta= 0.18; p<0.05$) and reduced activity ($\beta=0.23; p < 0.05$).

Dyspnea, a cardinal heart failure symptom, was related to several other heart failure symptoms. Dyspnea was observed by Ramasamy et al.\textsuperscript{40} ($r = 0.40$ df 46 p<0.01) and Sullivan et al.\textsuperscript{24} ($r = 0.43 – 0.56$, p < 0.001) to be related to depression. Bekelman et al.\textsuperscript{5} found 5:1 odds that an individual with probable depression would be quite a bit or very much distressed by shortness of breath compared to study participants who did not have depression (OR 5.28, p = .05). Redeker\textsuperscript{23} found a relationship between dyspnea and anxiety ($r = 0.22 – 0.35$, p = 0.001 – 0.02), however, Ramasamy et al.\textsuperscript{40} did not find a relationship between dyspnea and anxiety. Yu et al.\textsuperscript{38} observed an inverse correlation between dyspnea and the construct of anxiety/depression ($r = -0.17$, p < 0.05). Webel et al.\textsuperscript{41} observed moderate daily correlations between dyspnea and edema ($r = 0.45 – 0.63$, p < 0.001). Dyspnea was related to fatigue including the characteristics general fatigue,\textsuperscript{26-27} exertion fatigue\textsuperscript{26} and fatigue intensity.\textsuperscript{39} Paroxysmal nocturnal dyspnea was related to the sleep characteristics sleepiness ($r = 0.161$, p 0.02) and insomnia ($r = 0.279$, p = 0.004).\textsuperscript{42} Dyspnea had a non-significant relationship with sleep disturbance.\textsuperscript{40} The relationship between sleep disordered breathing and sleep quality or excessive daytime sleepiness was also non-significant.\textsuperscript{36}

Akomolafe, et al.\textsuperscript{43} and Sauve et al.\textsuperscript{44} did not detect a relationship between cognitive function and depression. Sauve et al.\textsuperscript{44} did not find that cognitive function was related to anxiety or pain. Some investigators document that individuals with heart failure have difficulty detecting symptoms of heart failure.\textsuperscript{45-47} Older individuals may require assistance with the detection and interpretation of their heart failure symptoms.\textsuperscript{48} Cameron, Worrall-Carter, Page, Riegel, Lo, and
Stewart\textsuperscript{49} observed that mild cognitive dysfunction is a predictor of the ability to independently recognize symptoms changes.

Using statistical procedures such as principal components analysis,\textsuperscript{50-52} confirmatory factor analysis,\textsuperscript{33} hierarchical cluster analysis,\textsuperscript{7,53,54} and structural equation modeling\textsuperscript{55} investigators developed the following relationships among 3 or more symptoms. Dyspnea was included in a cluster of symptoms in 6 studies.\textsuperscript{7,50,51,53-55} The characteristics of dyspnea that were observed in a cluster included orthopnea, paroxysmal nocturnal dyspnea, dyspnea on exertion, shortness of breath at rest, and shortness of breath at night. Two studies reported a symptom cluster composed entirely of characteristics of dyspnea.\textsuperscript{7,50} Five of the symptom clusters that included dyspnea also included fatigue\textsuperscript{50,51,53} or the dimensions of fatigue, increased need to rest\textsuperscript{54} and vital exhaustion.\textsuperscript{52} Sleep disturbance, sleep difficulty or sleep problems were included with dyspnea in 3 symptom clusters.\textsuperscript{51,53,54} Edema described as weight gain,\textsuperscript{50} leg edema,\textsuperscript{55} or bloating and swelling\textsuperscript{53} was also included in a symptom cluster. However, three investigators reported that edema, formed a cluster that was separate from other heart failure symptoms.\textsuperscript{7,50,54} Hertzog, et al.\textsuperscript{53} found that forgetfulness was included in a cluster with difficulty sleeping, fatigue, and four dimensions of shortness of breath. Hertzog, et al.\textsuperscript{53} also reported that dizziness was associated with shortness of breath with activity, shortness of breath at rest, bloating and swelling, fatigue, and depression. Jurgens et al\textsuperscript{50} identified a group of symptoms composed of feeling one’s heart beat become faster, feeling chest pain, having an upset stomach, and having a cough.

Three investigators identified heart failure symptom clusters primarily consisting of psychosocial or emotional symptoms.\textsuperscript{51,54,55} Depression was a component of all 3 of the heart failure symptom clusters. Worry was included in 2 of these symptom clusters.\textsuperscript{51,54} Fatigue and
vital exhaustion were each included in a symptom cluster that included sleep disturbance and depression. Jurgens et al. and Smith et al. observed that difficulty concentrating, was included in a heart failure symptom cluster with psychosocial or emotional symptoms.

In summary this systematic review points out relationships between symptoms experienced by individuals with heart failure that include depression, fatigue and dyspnea. Additionally, relationships between symptom characteristics were also observed. Cognitive impairment does not appear to have a relationship with the heart failure symptoms of depression, anxiety or pain. However, forgetfulness and difficulty concentrating appear in symptom clusters along with shortness of breath, fatigue, difficulty sleeping, worry and feeling depressed.

**Stability**

Stability may be indicated by the reproducibility of a symptom cluster across multiple patient samples. At this point in the study of heart failure symptom clusters, it is early to comment on the stability of a heart failure symptom cluster. However, there are several observations regarding the persistence of co-occurring heart failure symptom relationships. It is notable that there is similarity in the composition of specific heart failure symptoms in pairs and heart failure symptom clusters reported by several investigators. For example, depression and fatigue, depression and anxiety, and dyspnea and fatigue along with sleep disturbance were validated by several investigators. Observation of a symptom cluster in different settings is indicative of stability or the replicability of a symptom relationship. Although the studies included in this systematic review were conducted primarily in the outpatient setting*, some of the studies were conducted in the inpatient setting†. Time, which refers to the duration of association among the symptoms in a cluster, is a component of the stability of a symptom

*5,6,21 – 24, 26, 29, 34, 35, 41, 39, 43, 44, 50, 52, 53, 55.  
†7,25, 27, 30, 37, 38, 51.
cluster. The symptom pairs, pain and depression, anxiety and depression, and depression and fatigue were validated by studies conducted over the time period 2004 through 2010.

Instrument selection also appears to have an influence on the stability of relationships among heart failure symptoms and the persistence of the heart failure symptom clusters. For example, depression evaluated using the Short Form Geriatric Depression Scale, Beck Depression Inventory, the Center for Epidemiologic Studies Depression Scale (CESD) or the Profile of Mood States Depression/Dejection scale correlated with sleep \( (r = 0.402, p < 0.001) \), sleep disturbance \( (r = 0.39 - 0.53, p < 0.001) \), or fatigue \( (r = 0.34 - 0.64, p 0.001 - 0.01) \).

However, investigators reported that depression assessed using the Hospital Anxiety and Depression Scale (HADS) depression subscale was not related to sleep disturbance \( (r = 0.19 - 0.26, p 0.06 - <0.11) \), or excessive daytime sleepiness \( (r = -0.02, p 0.855) \). Chen, et al. observed a relationship between depression assessed using the HADS depression scale and fatigue assessed using the Piper Fatigue Scale \( (r = 0.5, p < 0.001) \). Ramasamy et al. and Redeker did not observe a relationship between depression, assessed using the HADS depression scale, and fatigue.

Seven of the 34 studies reported non-significant relationships between some or all of the symptoms studied. Four of these studies had sample sizes between 50 and 70 subjects and used Pearson’s correlation to detect symptom relationships. Two studies with sample sizes of 100 or more observed a low proportion of the symptoms of interest. For example, Akomolafe et al. who studied depression and cognitive impairment in a sample of 100 heart failure patients, reported that 23% of the sample had depression and 10% of the sample had cognitive impairment. This investigator did not detect a relationship between depression and cognitive impairment. Falk et al. who studied relationships between fatigue, anxiety and depression,
reported the prevalence of depression in the sample of 112 individuals with heart failure was 18% and the prevalence of anxiety was 10%. Nonsignificant relationships were observed between anxiety and the fatigue characteristics, general fatigue, physical fatigue, reduced activity and reduced motivation. A statistically significant relationship was detected between anxiety and mental fatigue. Falk et al.\textsuperscript{27} also detected non-significant relationships between depression and the fatigue characteristics, physical fatigue and mental fatigue. However, relationships were detected between depression and the fatigue characteristics, general fatigue, reduced activity, and reduced motivation. Redeker et al.\textsuperscript{36} did not detect relationships among symptoms studied in a sample of 170 individuals with heart failure in which the prevalence of the symptoms of interest was between 46% and 85%. The 3 studies with samples of 100 or more study participants employed regression analysis to examine symptom relationships.\textsuperscript{27, 36, 43} While there were statistically significant findings in these studies, a greater prevalence of a symptom in the sample would add credibility to the conclusions reached by the investigators.

As work on identification of heart failure symptom clusters progresses, it will be important to be aware of the symptom characteristics measured by the assessment tool selected to measure the symptoms of interest as well as the prevalence of the symptom in the sample. Perhaps findings of variation in symptom relationships realized by the use of different instruments to evaluate a symptom is leading symptom assessment for heart failure symptom cluster development toward an emphasis on symptom characteristics rather than overall symptom construct.

**Summary and Conclusions**

This systematic review of studies reporting about heart failure symptom relationships provides evidence of the existence of heart failure symptom clusters. Depression and anxiety,
depression and fatigue, depression and pain, fatigue and pain, dyspnea and depression, and
dyspnea and sleep are some symptoms for which relationships were established by investigators.
A notable finding of this systematic review is differences in relationships when symptom
characteristics are considered. For example, anxiety was related to mental fatigue but not to
general fatigue, physical fatigue, reduced activity or reduced motivation. There was an
association between depression and difficulty initiating and maintaining sleep, sleep quality and
sleep disordered breathing, however, depression was not related to severity of sleep disordered
breathing. Relationships between depression and sleep or fatigue did not persist when the HADS
depression scale was used to assess depression as opposed to when the Beck Depression
Inventory, CESD, or POMS depression/dejection scale were used to evaluate depression. These
findings suggests that as work on heart failure symptom cluster identification continues,
consideration should be given to examining relationships among the various symptom
characteristics in addition to relationships among general measures of the symptom. Studies that
define the phenotype of individual heart failure symptoms may be needed prior to the
identification of heart failure symptom clusters.

Symptom relationships between cognitive function and depression, anxiety or pain were
not detected by the investigators included in this systematic review. As work on isolation of
heart failure symptom clusters progresses investigators would be well advised to remember that
symptom detection may be difficult for individuals with heart failure and to consider the use of
instruments for symptom assessment in impaired individuals such as those available for pain
assessment in non-verbal individuals.

This systematic review adds to the body of work on the identification of heart failure
symptom clusters by providing some insight into the composition of heart failure symptom
clusters. Additional study is needed before the composition of heart failure symptom clusters can be defined. This study, however, provides some initial findings about heart failure symptom assessment for use in identification of heart failure symptom clusters. Advancing the science of heart failure symptom phenotyping and heart failure symptom cluster identification has the potential to lead to more effective interventions that target a group of symptoms rather than a single symptom. Decreasing the number of interventions a patient must employ to manage heart failure symptoms is one way to facilitate heart failure symptom self-management.
References


Summary and Implications

- This systematic review observed relationships among several heart failure symptom pairs, for example, depression and anxiety, depression and fatigue, depression and pain, fatigue and pain, dyspnea and depression, and dyspnea and sleep.

- This analysis reveals relationships among heart failure symptom characteristics, such as mental, physical, or exertion fatigue, suggesting that identification of the phenotype of individual heart failure symptoms may be informative.

- Symptom assessment in cognitively impaired individuals with heart failure may present a challenge to investigators’ attempts to identify heart failure symptom clusters.

- Instrument selection may influence the persistence of relationships among heart failure symptoms.
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<th>Symptom Relationships</th>
<th>STROBE Score</th>
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<tr>
<td>Akomolafe et al</td>
<td>Cross-sectional design 100 heart failure patients who were consecutively recruited from an inner-city physician practice, rural physician practice and an urban physician practice for a single-blinded, randomized, controlled trial to evaluate the effectiveness of a telemonitoring intervention. Sample age &lt;64 years - 39% 65-74 years -39% &gt; 75 years - 22% Gender - 64% female</td>
<td>multiple logistic regression</td>
<td>Mini-Mental Status Examination (not reported) Geriatric Depression Scale (not reported)</td>
<td>Depression and cognitive impairment OR 0.78, 95%, p=0.8.0</td>
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<td>Bean et al</td>
<td>Cross-sectional, correlational design 97 heart failure patients who were inpatients on the cardiology unit or an outpatient in the heart failure clinic of</td>
<td>Pearson's correlation</td>
<td>Hospital Anxiety and Depression Scale Anxiety scale α =.85 Depression scale α = .83</td>
<td>Anxiety and depression r = 0.74 p&lt;0.01</td>
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<td>Bekelman et al.(^5) (2007)</td>
<td>Cross-sectional design 60 participants recruited from outpatient cardiology clinics at an academic – affiliated community hospital and a tertiary care academic referral hospital. Median age 75 years 37% female</td>
<td>Logistic regression model</td>
<td>Memorial Symptom Assessment Scale – Short Form (not reported) Geriatric Depression Scale – Short Form (not reported)</td>
<td>Depression and shortness of breath – patients with probable depression were more likely to be quite a bit or very much distressed by shortness of breath Adjusted odds ratio 5.28 p = .05</td>
<td>17</td>
</tr>
<tr>
<td>Chen et al(^20) (2010)</td>
<td>Cross-sectional correlational design Convenience sample of 105 patients with diagnoses of heart failure recruited from outpatient clinics or cardiovascular units of 3 hospitals Mean age 65.2 years Gender – 35.2% female</td>
<td>Pearson product moment correlation coefficients</td>
<td>Piper fatigue scale ((\alpha = 0.85)) Hospital anxiety and depression scale ((\alpha = 0.78) for the global scale, (\alpha = 0.73) for the anxiety scale, (\alpha = 0.95) for the depression scale)</td>
<td>Depression and fatigue – (r = 0.5\ p &lt; 0.001) Anxiety and fatigue – (r = 0.49\ p &lt; 0.001)</td>
<td>21</td>
</tr>
<tr>
<td>Chung et al(^29) (2009)</td>
<td>Cross-sectional descriptive design 58 patient-spouse dyads recruited from cardiac</td>
<td>Pearson Product Moment Correlation</td>
<td>Brief Symptom Inventory - depressive symptom subscale (for patients (\alpha = .92), for</td>
<td>Depression and anxiety (r = .72\ p &lt; .001)</td>
<td>18</td>
</tr>
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<td>Citation</td>
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<tr>
<td>Evangelista et al(^2) (2008)</td>
<td>Cross-sectional correlational design 150 patients with HF recruited from a single outpatient heart failure clinic within a tertiary, university affiliated medical center Mean age 55 years Gender – 27.3% women</td>
<td>Correlation</td>
<td>Profile of Mood States – Fatigue subscale (α = 0.88) Beck Depression Inventory (not reported)</td>
<td>Depression and fatigue r = .576 p&lt;.001</td>
<td>15</td>
</tr>
<tr>
<td>Falk et al(^2) (2009)</td>
<td>(no study design reported) [cross-sectional] 112 patients hospitalized in a university hospital with CHF 112 hospitalized patients with CHF Mean age 77 years Gender – 40% women</td>
<td>Stepwise forward multiple regression</td>
<td>Multidimensional Fatigue Inventory – Swedish version (α ranged from 0.60 – 0.78) Hospital Anxiety and Depression Scale Anxiety α = 0.77 Depression α = 0.78 Symptom Distress Scale α= 0.79</td>
<td>General Fatigue Anxiety - R(^2) .049 F 6.1; β -.03 (ns) Depression R(^2) .145 F 21.2; β .30 (p&lt;.01) Physical Fatigue Anxiety – R(^2) .016 F 1.8; β -.07 (ns) Depression – R(^2) .056 F 6.8; β .14 (ns) Reduced Activity Anxiety R(^2) .010 F 0.9; B -.16 (ns) Depression R(^2) .178 F 23.0; β .37 (p&lt;.001) Reduced Motivation Anxiety – R(^2) .044 F 4.9 β.10 (ns)</td>
<td>18</td>
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<tr>
<td>Fink et al(2009)</td>
<td>Cross-sectional research design Convenience sample of 87 heart failure patients recruited from 2 urban medical center outpatient Heart Failure clinics. Mean age 57 years Gender – 56% female</td>
<td>Pearson correlations</td>
<td>Fatigue Symptom Inventory – Interference Scale $\alpha = .93$ Profile of Mood States Fatigue scale $\alpha = .90$ Depression scale $\alpha .93$</td>
<td>Depression – $R^2 .110 F 13.7; \beta .40 (p&lt;.001)$ Mental Fatigue Anxiety – $R^2 .254 F 36.2; \beta .39 (p&lt;.001)$ Depression – $R^2 .007 F 1.0 \beta -.01 (ns)$ Appetite and physical fatigue $\beta 2.6 t 2.7 (p&lt;.01)$ Nausea and general fatigue $\beta .18 t 2.0(p&lt;.05)$ Nausea and reduced activity $\beta .23 t 2.3 (p&lt;.05)$ Pain and general fatigue $\beta .22 t 2.4 (p&lt;.05)$ Pain and physical fatigue $\beta .22 t 2.3 (p&lt;.05)$ Breathing and general fatigue $\beta .30 t 3.4 p&lt;.001)$</td>
<td>15</td>
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</table>
| Goebel et al⁶     | Secondary analysis 96 veterans who were outpatients at two hospitals and six affiliated community sites  
|                  | Mean age 67.2 years  
|                  | Gender – 4.2% female                                                               | Pearson coefficient correlations    | Brief Pain Inventory – pain severity scale α 0.91  
|                  | Patient Health Questionnaire – 2 (not reported)  
|                  | Generalized Anxiety Disorder – 2 (not reported)                                     | Depressi on and pain r = 0.32 p = 0.002  
|                  | Anxiety and pain r = 0.33 p = 0.001                                               | 20                                  |
| Hertzog et al⁵³   | Study design not reported  
|                  | 139 respondents recruited from patients receiving care at an outpatient heart failure clinic  
|                  | Mean age 70.6 years  
|                  | Gender – 24% women                                                                  | Hierarchical cluster analysis,      | Kansas City Cardiomyopathy Questionnaire α ranged from .78 to .89 except for self-efficacy which had an estimate of only .57  
|                  | 2) Shortness of breath at rest, with activity, lying down, at night, fatigue, difficulty sleeping, forgetfulness  
|                  | 3) Fatigue, shortness of breath with activity, shortness of breath at rest, dizziness, bloating and swelling, depression  
|                  | Heart Failure Symptom Survey (not reported)                                         | Clusters                            | Depression and anxiety  
|                  | State A – r = 0.52 p<0.01  
|                  | Trait A – r= 0.59, p <0.01                                                         | 19                                  |
| Jaing et al⁵⁰     | Secondary analysis 291 heart failure patients admitted to the cardiology service of a university medical center  
|                  | Mean age 63 years  
|                  | 45.8% women                                                                         | Pearson coefficient                 | Beck Depression Inventory (not reported)  
|                  | Spielberger State – Trait Anxiety Inventory (not reported)                          | Depression and anxiety State A – r = 0.52 p<0.01  
|                  |                                                                                     | Trait A – r= 0.59, p <0.01                                                         | 19                                  |
| Johansson et al⁵⁵ | Study design not reported  
|                  | 331 subjects chosen                                                                 | Principal component analysis with   | Uppsala Sleep Inventory (not reported)  
|                  |                                                                                     | Clusters                            | Mean O₂ saturation, dyspnea, NYHA class III, leg edema  
<p>|                  |                                                                                     | 19                                  |</p>
<table>
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<tr>
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<tbody>
<tr>
<td>Jurgens et al(^{50}) (2006)</td>
<td>from a previously investigated cohort of individuals living independently in a rural municipality Mean age 78 years 51% women</td>
<td>oblique rotation Structural equation modeling (SEM) Exploratory factor analysis Confirmatory factor analysis</td>
<td>Epworth Sleepiness Scale (not reported) Hospital Anxiety Depression Scale - Depression Scale(not reported) Dyspnea was assessed using a graded scale – 0 = no dyspnea, 10 = very severe dyspnea Polygraphic studies in the patient’s home</td>
<td>2) Excessive daytime sleepiness, fatigue, depression, non-restorative sleep</td>
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<tr>
<td>Jurgens et al(^{51}) (2009)</td>
<td>Instrument Development Convenience sample of 201 community dwelling participants recruited from an urban tertiary care hospital, a suburban tertiary care hospital and a community hospital Mean age 70 years 44% female</td>
<td>Exploratory factor analysis using a principle component analysis with varimax rotation.</td>
<td>Heart Failure Somatic Awareness Scale (theta reliability = 0.71) Spielberger Trait Anxiety Inventory Form (not reported)</td>
<td>Factor 1 – orthropnea, dyspnea, paroxysmal nocturnal dyspnea Factor 2 – my feet were swollen, my shoes were tighter than usual Factor 3 – I could feel my heart beat faster, I felt pain in my chest, I had an upset stomach, I had a cough Factor 4 – fatigue, weight gain, dyspnea on exertion, unable to catch my breath</td>
<td>20</td>
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<tr>
<td>Jurgens et al(^{51}) (2009)</td>
<td>Secondary Analysis 687 hospitalized patients with a confirmed diagnosis of heart failure drawn from a data registry of</td>
<td>Principal component analysis with oblique rotation Logistic</td>
<td>Minnesota Living with Heart Failure Questionnaire (Bartlett’s Test of Sphericity was reported as “acceptable”)</td>
<td>Inter-item correlation depression and worry .64 Inter-item correlation shortness of breath and fatigue low energy .65 Symptom Clusters Acute volume overload – shortness</td>
<td>21</td>
</tr>
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</table>
| the Heart Failure Quality of Life Trialist Collaborators.  
Mean age 71 years  
Gender – 51.7% female | Regression                                                                              |                         | of breath, tired, fatigue low energy, sleep problems  
   Emotional cluster – depressed, worry, difficulty concentrating or remembering things  
   Chronic volume overload – swelling, increased need to rest, dyspnea on exertion |                                                        |              |
| Lee et al\(^\text{m}\)  
(2010)  
Secondary Analysis  
331 patients. Data for this study were compiled from 3 prospective, longitudinal studies that had similar inclusion and exclusion criteria.  
Mean age 61 years  
Gender – “predominately male” | Cluster Analysis - hierarchical cluster agglomerative approach  
Minnesota Living With Heart Failure Questionnaire (α .89) |                         | Physical Symptom Cluster – dyspnea, fatigue increased need to rest, fatigue low energy, sleep disturbance  
Emotional/Cognitive Symptom Cluster – worrying, feel depressed, cognitive problems | 17               |
| Lesman-Leegte et al  
(2006)  
Secondary analysis of data from a randomized control trial  
572 patients hospitalized with heart failure  
Mean age 71± 12 years  
38% women | Multivariable logistic regression  
Center for Epidemiological Studies Depression Scale (not reported)  
Heart Failure symptoms were assessed by interview using 10 structured questions |                         | Depression and sleep – odds ratio = 3.45, p 0.001  
Depression and loss of appetite – odds ratio = 2.28 95%, p = 0.001. | 18               |
<table>
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<tr>
<td>Luyster et al\textsuperscript{31} (2009)</td>
<td>Cross-sectional design 88 patients with a primary diagnosis of heart failure and treated with an ICD who were recruited from a large cardiology practice Mean age 70 years 23% female</td>
<td>Pearson correlation</td>
<td>Beck Depression Inventory (not reported) State-Trait Anxiety Inventory – Trait (not reported)</td>
<td>Depression and anxiety $r = 0.66 \ p&lt;.01$ Depression and dietary adherence $r = -0.51 \ p&lt;.01$</td>
<td>15</td>
</tr>
<tr>
<td>Paukert et al\textsuperscript{32} (2009)</td>
<td>Study design not reported 104 Heart Failure patients identified using the outpatient and patient treatment databases of a large VA hospital Mean age 71.7 years Gender – 1% female</td>
<td>Spearman's rho correlations Pearson product-moment correlations</td>
<td>Geriatric Depression Scale (not reported) Geriatric Anxiety Inventory (not reported)</td>
<td>Depression and anxiety $r=0.65 \ p&lt;0.01$</td>
<td>16</td>
</tr>
<tr>
<td>Principe-Rodriguez et al\textsuperscript{42} (2005)</td>
<td>Design not reported 201 participants who were new patients referred to the heart failure program at a university hospital Mean age 57.7 years 48% women</td>
<td>Pearson coefficient</td>
<td>Cleveland Sleep Habits Survey (not reported)</td>
<td>Paroxysmal nocturnal dyspnea and sleepiness $r = 0.161 \ p = 0.02$ Paroxysmal nocturnal dyspnea and insomnia risk $r = -0.279 \ p = 0.004$</td>
<td>19</td>
</tr>
<tr>
<td>Ramasamy et al\textsuperscript{40} (2006)</td>
<td>Study design not reported 67 individuals with</td>
<td>Pearson's product moment</td>
<td>Dyspnea Scale (not reported) Hospital Anxiety and</td>
<td>Depression and dyspnea $r=0.40 \ df \ 46 \ p&lt;0.01$ Depression and sleep disturbance</td>
<td>14</td>
</tr>
<tr>
<td>Citation</td>
<td>Design/Sample/Setting</td>
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<td>chronic, non-valvular heart failure who were well-compensated ambulatory patients or recently hospitalized with decompensated heart failure. Mean age 65.4 years Gender – 32% women</td>
<td>correlations</td>
<td>Depression Scale (not reported) Abbreviated visual-analog scale to assess severity of fatigue (0-10, not at all to a great deal) (not reported) A questionnaire about perception of health status adapted from the general health items on the SF-36 Sleep questionnaire adapt from the Generalized Anxiety Disorder module of the Structured Clinical Interview for DSM-IV Axis 1 Disorders (not reported)</td>
<td>r = 0.26 df 41 p&lt;0.11 Anxiety and dyspnea r=-0.04 df 46 p&lt;0.77 Fatigue and dyspnea r= 0.62 df 36 p&lt;0.01 Dyspnea and sleep disturbance r = 0.26 df 41 p&lt;0.11 Dyspnea and fatigue r = 0.62 df 36 p &lt;0.01 Depression and fatigue – correlation was not statistically significant.</td>
<td>18</td>
</tr>
<tr>
<td>Redeker²³ (2006)</td>
<td>2 group cross-sectional design 61 HF patients recruited from an outpatient heart failure program and 57 comparison group participants recruited from the surrounding community</td>
<td>Bivariate correlations</td>
<td>Centers for the Epidemiological Studies of Depression (α = .88) Profile of Mood States – Short Form Dejection (Depression scale α = .92, Tension Anxiety scale α = .88) Hospital Anxiety and Depression CESD r = 0.41, p&lt;.001 Depression POMS DD r=0.17 p 0.70 Depression HADS r=0.03 p .790 Fatigue Depression CESD r=.57 p&lt;.001 Depression POMS DD r=.34 p&lt;.001 Depression HADS r=.01 p .953</td>
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<tr>
<td>Redeker et al. (2010)</td>
<td>Cross-sectional observational study of 173 stable chronic heart failure patients recruited from 5 heart failure disease management programs. Mean age 60.3 years.</td>
<td>Logistic Regression, Confirmatory factor analysis</td>
<td>Multi-Dimensional Assessment of Fatigue (α = .91 Center for Epidemiological Studies Depression Scale (α = .89) Epworth Sleepiness</td>
<td>Patients with difficulty initiating and maintaining sleep were more likely to be depressed. OR = 5.09 95% CI = 2.41 – 10.75. “The latent variable daytime symptoms (fatigue, depression, and excessive daytime sleepiness) had high factor loadings on fatigue (0.724.</td>
<td>20</td>
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</table>

Mean age of the heart failure group 58.7 years Mean age of the comparison group 55.25 years Gender – Heart failure group 37.7% women, comparison group 52.6% women 61 HF patients and ...
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<th>Symptom Relationships</th>
<th>STROBE Score</th>
</tr>
</thead>
</table>
| Redeker et al (2010) | Cross-sectional observational design 170 patients with stable chronic HF recruited from 5 structured disease management programs  
.gender – 35.5% women | Linear and logistic regression | 6 minute walk test  
.epworth sleepiness scale (α = .77)  
multi-dimensional assessment of fatigue (α = .93)  
.center for epidemiological studies depression scale (α = .84)  
pittsburgh sleep quality index (α = .79)  
wrist actigraph to measure daytime mobility  
nocurnal polysomnography | Depression and severity of sleep disordered breathing – no statistically significant relationship  
fatigue and severity of sleep disordered breathing – no statistically significant relationship  
sleep quality and severity of sleep disordered breathing – no statistically significant relationship  
Excessive daytime sleepiness and severity of sleep disordered breathing – no statistically significant relationship | 19 |
<table>
<thead>
<tr>
<th>Citation</th>
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</thead>
</table>
| Sauve et al 44 (2009) | Case-control design 50 patients with heart failure recruited from heart failure and cardiology clinics of a university hospital and 50 controls recruited from active adult communities  
Mean age: Heart failure patients 63 years, Controls 62 years.  
Gender: Heart failure patients 48% female, Controls 54% female | Pearson's r correlation, Kendall tau | Neurobehavioral Cognitive Status Examination  
Symbol-Digit Modalities Test  
Rey Auditory Verbal; Learning Test (not reported)  
Controlled Word Association Test (not reported)  
Finger Tapping Test (not reported)  
Memory Scanning Test (not reported)  
Visual Scanning Task (not reported)  
WAIS-R Vocabulary Subtest (not reported)  
The Mental Health Index (not reported)  
Short Form – 36 (not reported) | No statistically significant relationships between  
Depression and orientation  
Depression and attention  
Depression and memory  
Depression and motor performance  
Anxiety and orientation  
Anxiety and attention  
Anxiety and memory  
Anxiety and motor performance  
Pain and orientation  
Pain and attention  
Pain and memory  
Pain and motor performance | 15           |
| Skobel et al 34 (2005) | Study design not reported  
51 patients of an ambulatory clinic referred for evaluation of heart failure or consideration for a | Spearman rank correlation coefficients | Beck Depression Inventory (not reported)  
Pittsburg Sleep Quality Index (not reported)  
SF 36 – German version (not reported) | In heart failure patients with sleep disordered breathing  
Depression and sleep quality  
$r = 0.71$ p = 0.001  
Depression and apnea hypopnea index  
r = 0.88 p = 0.001  
Pain and apnea hypopnea index | 15           |
<table>
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<tbody>
<tr>
<td>Smith et al²²</td>
<td>Prospective study design 381 CHF patients from an outpatient heart failure clinic Mean age 65.7 ± 10.4 years Gender 27.8% female</td>
<td>Principal component analysis with oblimin rotation, latent class cluster analysis</td>
<td>Maastricht questionnaire (not reported) Minnesota Living with Heart Failure Questionnaire (not reported)</td>
<td>Clusters 1) Absence of vital exhaustion 2) Manifest vital exhaustion, relative absence of cognitive affective, depressive symptoms, relative absence of sleep difficulties, decreased concentration, increased levels of fatigue 3) Manifest vital exhaustion, cognitive affective depressive symptoms, sleep difficulties</td>
<td>15</td>
</tr>
<tr>
<td>Smith et al²⁶</td>
<td>Prospective study design 136 CHF patients from an outpatient heart failure clinic Mean age 65.6 years Gender - 23.5%</td>
<td>Pearson’s product moment correlation coefficients</td>
<td>Dutch Exertion Fatigue Scale (not reported) Fatigue Assessment Scale (not reported) Health Complaints Scale somatic complaints</td>
<td>Exertion Fatigue and: Sleep problem  ( r = .29 \ p = .001 ) Dyspnea  ( r = .33 \ p &lt; .001 ) Cardiac pain  ( r = .42 \ p &lt; .001 ) Depressive symptoms  ( r = .33 \ p &lt; .001 ) General Fatigue and: Sleep problem  ( r = .42 \ p &lt; .001 )</td>
<td>16</td>
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<tr>
<td>Song et al (2010)</td>
<td>Prospective Study 421 heart failure patients recruited during an index hospitalization chronic heart failure exacerbation at tertiary medical centers Mean age 62 39.7% female</td>
<td>Agglomerative hierarchical clustering approach with Ward's method,</td>
<td>Memorial Symptom Assessment Scale – Heart Failure (α = .81)</td>
<td>Dyspnea r = .45 p&lt; .001 Cardiac pain r = .44 p&lt;.001 Depressive symptoms r = .42 p&lt;.001</td>
<td>17</td>
</tr>
<tr>
<td>Stephen et al (2008)</td>
<td>Descriptive, cross-sectional and correlational design Convenience sample of 53 patients with a diagnosis of HF and with documented systolic dysfunction recruited from outpatient clinics Mean age 77 years 32% women</td>
<td>Pearson product moment correlations</td>
<td>Profile of Mood States fatigue scale (α = .82) Visual analogue scale for fatigue (not reported) Revised symptom checklist (not reported)</td>
<td>Fatigue Intensity and Breathless with activity r = .25 p&lt;.05 Fatigue Intensity and Difficulty sleeping r = .20 p&gt;.05 Fatigue Intensity and nocturia r = .36 p&lt;.01</td>
<td>19</td>
</tr>
<tr>
<td>Sullivan et al (2004)</td>
<td>Prospective design 142 subjects and 88 spouses provided</td>
<td>Partial correlations</td>
<td>Hamilton Depression Rating Scale (not reported)</td>
<td>Baseline/ Follow-up Correlations Depression and bodily pain -.37 p&lt;.001/-.47 p&lt;.001</td>
<td>21</td>
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<tr>
<td>Tang et al.25 (2010)</td>
<td>Cross-sectional correlation design Convenience sample of 107 CHF patients recruited from a cardiology ward of a medical center Mean age 69.3 years Gender – 46.7% women</td>
<td>Pearson correlations</td>
<td>Tang Fatigue Rating Scale (total scale – α = .96, physiological scale – α = .83, psychosocial scale – α = .92, daily-living activities – α = .97) Fatigue Visual Analog Scale (total scale α = .89, energy subscale α = .97, fatigue subscale α = .89) Beck Depression Inventory (α 0.81)</td>
<td>Depression and fatigue r=0.77 p&lt;0.01</td>
<td>22</td>
</tr>
<tr>
<td>Wang et al.35 (2010)</td>
<td>Predictive correlational design</td>
<td>Pearson product</td>
<td>Perceived Health Scale (α = .73)</td>
<td>Depression and sleep quality r = .402 p&lt;0.001</td>
<td>21</td>
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<td>Convenience sample of 101 patients with heart failure recruited from cardiology clinics Mean age – 74 years Gender 32.8% female</td>
<td>moment correlations</td>
<td>Short Form Geriatric Depression Scale ($\alpha = .82$) Pittsburg Sleep Quality Index ($\alpha = .80$)</td>
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<tr>
<td>Webel et al$^{41}$ (2007)</td>
<td>Descriptive correlational design 48 heart failure patients who were referred to the investigators by cardiologists and nurse practitioners- data collected for 30 days. Mean age 48± 15 years Gender – 46% female</td>
<td>Spearman correlation coefficients</td>
<td>Symptom Rating Scales – 10 point analog scale with 0 indicating absence of dyspnea or edema and 10 indicating the worst dyspnea or edema (not reported)</td>
<td>Dyspnea and edema – correlations calculated for each day of a 30 day period ranged from 0.45 to 0.63 $p &lt; 0.001$ for all correlations</td>
<td>15</td>
</tr>
<tr>
<td>Yu et al$^{38}$ (2004)</td>
<td>Cross-sectional study design. 227 patients with an index diagnosis of CHF were recruited from a medical unit of a university-affiliated hospital Mean age 77.1 years 52.4% women</td>
<td>Pearson product-moment correlation</td>
<td>Hospital Anxiety and Depression Scale – Chinese version (not reported Chronic Heart Failure Questionnaire dyspnea and fatigue subscales - Chinese version (not reported)</td>
<td>Anxiety/Depression and dyspnea $r = -.17 p &lt; .05$ Anxiety/Depression and fatigue $r = -.50 p &lt; .001$</td>
<td>16</td>
</tr>
</tbody>
</table>
Figure 1. Search and Screening Results

1277 studies identified through database searches

39 studies identified through ancestor search

1316 studies after duplicates removed

1237 studies excluded because they included conditions in addition to heart failure, evaluated the efficacy of an intervention for the treatment of heart failure or did not examine relationships among individual heart failure symptoms.

79 studies screened and assessed for eligibility

45 studies excluded because they did not provide information about a statistical relationship among heart failure symptoms

34 studies included in the systematic review
Heart Failure Symptom Clusters and Functional Status

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6 Tables; 1 Figure
Abstract

Background: Clinical assessment of heart failure includes symptom identification and the evaluation of the relationship of symptoms to functional status. Symptom clusters are groups of at least 2 or 3 co-occurring symptoms that are related but are independent of other groups of symptoms. Since the publication of the NYHA functional classification symptom occurrence in cardiac conditions has been linked to functional status.

Objectives: The objectives of this study are to: (1) examine relationships among symptoms commonly experienced by individuals with heart failure, (2) identify symptoms that form clusters, and (3) evaluate the impact of heart failure symptom clusters on attributes of functional status: limitations and mobility.

Methods: The Theory of Unpleasant Symptoms guided the conduct of this study. A convenience sample of individuals (n = 117) with a confirmed diagnosis of heart failure was recruited from an academic medical center. Prevalent symptoms (anxiety, depression, dyspnea, peripheral edema, pain, appetite, hunger, cognitive dysfunction and daytime function) were evaluated along with the outcome variables, functional limitations and mobility. Principle components analysis was used to extract symptom clusters and regression analysis was used to evaluate the relationship between the symptom clusters, their interaction terms, and the demographic variables, age and co-morbidity.

Results: Three symptom clusters, sickness behavior, discomforts of illness, and GI distress were extracted. Predictors of functional limitations (F = 35.96, p = 0.0005, R^2 = 0.578) included sickness behavior (β = -.681, p ≤ 0.0005), discomforts of illness (β ≤ -.765, p = 0.0005) and the interaction term between these two symptom clusters (β = .649, p ≤ 0.014). This model predicted 59% of the variance in functional limitations. Predictors of limited mobility (F =
20.68, \( p = 0.0005, R^2 = 0.275 \) included sickness behavior (\( \beta = -0.441, p \leq 0.0005 \)) and co-morbidity (\( \beta = -0.200, p \leq 0.019 \)). This model predicted 28% of the variance in mobility.

**Conclusions:** Discomforts of illness and sickness behaviors were strong predictors of functional limitations. Functional limitations increase as discomforts of illness increase, but increases at a faster rate when sickness behaviors are increased. Sickness behavior and co-morbidity were predictors of limited mobility. Symptom management strategies focused on the symptom clusters may improve functional limitations and mobility for individuals experiencing heart failure symptoms.
Background

Heart failure is a progressive clinical syndrome that is estimated to affect approximately 6.6 million Americans over age 18 years and is projected to increase by 3 million people by 2030. The ongoing clinical assessment of individuals with heart failure includes symptom identification and evaluation of the relationship of symptoms to functional status. Symptoms have been referred to as threats to health and a stimulus for entry into the medical system.

Symptoms may occur singly or in clusters of two or more. Dodd, Miaskowski and Paul and Kim, McGuire, Tulman and Barsevick characterize symptom clusters as a group of at least 2 or 3 symptoms that co-occur, are related but are independent of other groups of symptoms. The symptoms in a symptom cluster may be related to a common source such as a disease, treatment, life transition, or co-morbid conditions. Concurrence, stability, and relationship are important characteristics of a symptom cluster.

The influence of a symptom cluster on one or more patient outcomes may be useful in determining whether a symptom cluster is clinically significant. Since 1928, when the New York Heart Association (NYHA) published a classification of clinical cardiac disease severity based on the occurrence of symptoms with physical activity, functional status has been associated with symptoms of cardiac disease. Leidy and Wang concur that the term functional status refers to activities performed to meet basic needs, carry out usual roles, and maintain health and well-being. Additionally, Wang proposes that functional status is demonstrated by the performance of activities including physical, psychological, social, spiritual, intellectual, and roles associated with daily living.

In the heart failure patient population, relatively few studies have been conducted to identify symptom clusters. Fatigue and dyspnea is a pair of symptoms that have been included in
clusters reported by several investigators. For example, fatigue and dyspnea are included in symptom clusters with forgetfulness, sleep disturbance, dizziness, and depression, and manifestations of edema such as weight gain and swelling. Dyspnea, dizziness, swelling and bloating formed a symptom cluster with fatigue and depression. Associations between fatigue and pain and appetite loss are also reported by investigators conducting studies of single symptoms but they have not appeared in the heart failure symptom clusters reported at this point.

The relationship between fatigue and depression has been supported by several investigators. A cluster of symptoms which include fatigue, depression, and daytime sleepiness has been identified by Riegel and Ratcliff and is characterized as sickness behavior. As well, fatigue and depression have both been included in a symptom cluster with sleep disturbances such as non-restorative sleep, excessive daytime sleepiness and sleep difficulties. Investigators have also observed that depression and anxiety have been included in symptom clusters with cognitive problems.

Evaluation of the clinical significance of a symptom cluster may include an assessment of the effect of the symptom cluster on important patient outcomes. For example, investigators have observed these relationships with outcomes such as death, re-hospitalization, health status, and global perceived health. In individuals with NYHA class IV heart failure, the sickness behavior symptom cluster was a predictor of the risk of death or hospitalization. The relationship between a cluster of heart failure symptoms and functional status is not reported in the literature.

The purpose of this study is to examine the presentation of symptom clusters in individuals who have heart failure and evaluate the relationship of the identified clusters to
functional status in these individuals. Specific aims are to: (1) examine symptoms commonly experienced by individuals with heart failure, (2) identify symptoms that form clusters, and (3) evaluate the impact of heart failure symptom clusters on two attributes of functional status: limitations and mobility.

**Conceptual Framework**

The Theory of Unpleasant Symptoms (TUS) illustrates the experience of concurrent symptoms. In a symptom cluster, concurrence refers to symptoms occurring together—for example, the occurrence of dyspnea, fatigue, and edema in an individual who has heart failure. The relationship among symptoms portrayed by the TUS is described as multiplicative instead of additive and symptoms may interact to augment the effects of each other. For example, several symptoms may individually have limited effect on an outcome, whereas, in a cluster, the impact may be highly significant. Model concepts included in the TUS are influencing factors that may trigger or shape the symptom experience (e.g., age and co-morbidities), symptoms experienced by an individual (e.g., dyspnea, fatigue, edema, sleep and cognitive disturbances, pain, anxiety, depression, hunger and appetite disturbances), and the consequences of the symptom experience (functional and mobility limitations). Consequences of the symptom experience are performance-related and are hypothesized to include effects on physical activity, activities of daily living, social activities, and role performance. The conceptual framework for this study, based on the TUS, is presented in Figure 1.

**Methods**

**Design, sample and setting**

A convenience sample of individuals (n=117) with a confirmed diagnosis of heart failure was recruited from the Heart Failure/Heart Transplant Program of Virginia Commonwealth
University. Potential participants in this cross-sectional study were 18 years of age or older, NYHA functional class II – IV, had been receiving standard therapy for heart failure for at least 3 months prior to enrollment, and were able to speak and read English well enough to complete the questionnaires. Standard therapy for heart failure includes beta blocker therapy, diuretics, and angiotensin converting enzyme inhibitor therapy. Therapy for patients with symptomatic heart failure who have reduced left ventricular ejection fraction (<35%), a history of cardiac arrest, ventricular fibrillation or hemodynamically destabilizing ventricular tachycardia may also include an implantable cardioverter-defibrillator.

**Data collection procedures**

The study was approved by the Virginia Commonwealth University Institutional Review Board. After obtaining informed consent, study participants received a study packet containing a cover letter with instructions about completing the study materials, a copy of the consent form, and the study questionnaires. Study staff reviewed the contents of the packet with each participant and answered questions about completion of the questionnaires. Participants completed the questionnaires on the day of their clinic visit.

**Measurement of Variables**

Demographic variables (gender, age, education, employment and marital status) were self-reported on a demographic questionnaire. Clinical characteristics (NYHA functional classification of heart failure, ejection fraction [EF], etiology of heart failure, time since diagnosis of heart failure, prescribed medications, and co-morbidities) were collected from the medical record. The Charlson Co-morbidity Index, which provides a weighted taxonomy of co-morbid conditions with prognostic implications, was used to summarize co-morbid conditions.
Dyspnea was measured using the shortness of breath subscale of the Cardiovascular Limitations and Symptoms Profile (CLASP). The subscale consists of 5 questions assessing patient perception of shortness of breath. Scale items evaluating frequency, severity, and interference with activities are categorized as mild, moderate or severe (1=mild, or not at all;5 =severe, or a greater frequency). In individuals with coronary heart disease, internal consistency reliability, reported by Lopez, Chair, Thompson, Tsui, and Lewin, is 0.70 for the CLASP and 0.82 for the shortness of breath subscale. In the present study, Cronbach’s alpha for the shortness of breath subscale was 0.85.

Fatigue was evaluated using the Brief Fatigue Inventory which is composed of 9 items-three items assessing fatigue severity and 6 items assessing the amount of interference with aspects of life associated with fatigue. Items are rated on a 0 (no fatigue) to 10 (fatigue as bad as you can imagine) scale. Cronbach’s alpha for the Brief Fatigue Inventory is reported to be 0.96. In this study, internal consistency reliability was 0.95.

Consistent with the strategy used by Webel and colleagues to evaluate daily variation of edema in heart failure patients, a visual analogue scale was selected to assess peripheral edema. The scale was anchored by the descriptors none (0) and worst I have ever had (10). Study participants were also asked to report the location of their edema (1=feet and ankles; 2=up to the knees; 3=above the knees).

The Hospital Anxiety and Depression Scale (HADS) was used to assess anxiety and depression. The HADS is designed to provide reliable screening for clinically significant anxiety and depression. Each subscale is composed of 7 items on a 4-point Likert scale (0=absence; 3=occurrence most of the time). Chen et al. reported Cronbach’s alpha for the HADS to be 0.78. Internal consistency reliability for the anxiety and depression subscales was 0.73 and 0.95,
respectively. Cronbach’s alpha for the HADS in this study is 0.89 and for the anxiety and depression subscales, 0.84 and 0.81, respectively.

The Bodily Pain Scale of the Medical Outcomes Study (MOS) 36 – Item Short-Form Health Survey (SF-36) was selected to evaluate pain. The 4 items assess the frequency of bodily pain or discomfort and the extent of interference with normal activities. Item responses range from 1 indicating none or very mild to 5 indicating frequent occurrence or very severe. M’Horney, Ware and Raczek reported a reliability of 0.77 for the SF-36 Bodily Pain Scale. In this study Cronbach’s alpha for the Bodily Pain Scale was 0.83.

Appetite, the psychological desire for certain foods, and hunger, a physical sensation indicating the need to eat, were assessed using two items of the Food, Eating Experiences, and Diet (FEED) instrument. The two items included visual analogue scales measuring hunger and appetite (1 = no hunger sensations or no appetite/cravings; 10 = hungriest I have ever been or my appetite was extremely good/strong cravings).

The General Sleep Disturbance Scale is composed of 21 items evaluating initiation insomnia, maintenance insomnia, sleep quality, sleep quantity, daytime functioning, and medication/self help for sleep. Responses to each item are captured using an 8 point Likert scale (0 = no days; 7 = every day). A Cronbach’s alpha of 0.88 has been reported for the instrument. In this study, only the daytime functioning subscale (5 items) was used. Excessive daytime sleepiness, a consequence of sleep disturbance, was chosen as a variable in this study because of its prevalence in individuals with heart failure and association with worse functional status and lack of physical activity. In the present study, Cronbach’s alpha on this subscale was 0.74.

Cognitive impairment was assessed using the MOS Cognitive Function Scale, which provides an assessment of the day-to-day difficulties with cognitive functioning of which an
individual has awareness. The 6-item Likert scale (1=all the time; 6=none of the time) was re-coded so that higher scores reflected more difficulty with cognitive functioning. Hays, Sherbourne and Mazel\textsuperscript{41} reported Cronbach’s alpha for the Cognitive Function Scale is 0.88. Cronbach’s alpha was 0.91 in this study.

The outcome variable, functional status, conceptualized as functional limitations and mobility limitations, was evaluated using the MOS Physical Functioning Scale.\textsuperscript{42} Categories of activities in this evaluation of functional status include self-care limitations, mobility, and physical activities. There are 10 items that evaluate physical limitation (1=limited a lot, 2=limited a little, 3=not limited at all), and 3 items addressing mobility or independence in physical activity (1 = difficulty all of the time or every day, 5 = difficulty none of the time or never). Hays, Sherbourne and Mazel\textsuperscript{41} reported a Cronbach’s alpha of 0.93 for the physical limitations scale and 0.74 for the mobility scale. In this study Cronbach’s alpha for the physical limitations subscale was 0.91 and for the mobility subscale Cronbach’s alpha was 0.65.

**Statistical Analysis**

Data were analyzed using descriptive statistics, Pearson’s correlations, principle components analysis, and multiple regression analyses. The level of significance was set at $p<0.05$. Histograms and scatter plots of variables were examined for skew, gaps in distribution of the data, multiple peaks, and outliers. We examined the frequency and percent of symptoms to confirm prevalence and co-occurrence. Correlation analysis using Pearson’s $r$ was used to confirm that the symptoms were related. The study sample was characterized using demographic and clinical variables. Means and standard deviations are reported for continuous variables and frequencies and percents are reported for categorical variables.
Principle components analysis (PCA) was used to identify symptoms forming clusters. To improve interpretability, we used oblimin rotation with Kaiser normalization. A 3-component solution was obtained. Loadings were evaluated to determine the symptoms retained on each component. After identification of the symptom clusters—characterized as sickness behaviors (5 symptoms), discomforts of illness (3 symptoms), and gastrointestinal (GI) distress (2 symptoms)—a composite score was calculated for each symptom cluster. This score was calculated by multiplying each symptom (scale/subscale) mean by the loading and summing the products of the calculation.

Assumptions of regression (normality of residuals and homogeneity of variance) were examined and two multiple regression analyses were performed with functional limitations and mobility as the dependent variables of each respective analysis.

**Results**

**Sample characteristics**

Participants (n=117) were 62% male and had a mean age of 56 years. A little less than half (42%) were receiving disability. Etiology of heart failure was primarily ischemic (48%) or idiopathic (43%). Mean EF was 25%. On average, time since the onset of heart failure was 5 years. The majority of the study participants were NYHA functional class 2 (44%) or class 3 (39%) and 13% were class 4. The most prevalent co-morbidities were diabetes mellitus (44%), renal disease (32%), chronic pulmonary disease (28%), and connective tissue disease/arthritis (21%). Twenty six participants (13.6%) had only heart failure. Over half of the study participants (62%) had an implanted cardiac defibrillator (ICD); 9% were receiving intravenous inotrope infusions; 21 were either listed or being evaluated for heart transplantation, and 10 were
being evaluated for mechanical circulatory support. Demographic and clinical characteristics are presented in Table 1.

All of the individuals in this study reported having shortness of breath at least once or twice during the previous 2 weeks. Some other symptoms with a high prevalence in this sample of individuals with heart failure are decreased hunger (95%), decreased appetite (85%), fatigue (73%), edema (73%), and pain (62%). Symptom prevalence is presented in Table 2.

**Principal Components Analysis (PCA)**

The PCA solution revealed 3 symptom clusters, characterized as sickness behaviors (5 symptoms), discomforts of illness (3 symptoms), and gastrointestinal (GI) distress (2 symptoms). The factor loadings are presented in Table 3. In Table 4 descriptive statistics for the model variables are presented for each cluster. Descriptive statistics for the symptom cluster composite scores may be found in Table 5.

**Sickness Behavior.** The sickness behavior cluster (mean=58.89; SD=25.16) was composed of anxiety, depression, daytime functioning, cognitive dysfunction, and fatigue. The most highly correlated among these symptoms are depression and fatigue \((r = 0.652, p \leq 0.0005)\) and depression and anxiety \((r = 0.648, p \leq 0.0005)\). Depression was correlated at the same level with daytime function \((r = 0.513, p = 0.0005)\) and cognitive dysfunction \((r = 0.513, p \leq 0.0005)\). Cognitive dysfunction was inversely correlated with anxiety \((r = -0.567, p \leq 0.005)\), fatigue \((r = -0.469, p \leq 0.0005)\) and daytime function (sleepiness) \((r = -0.432, p \leq 0.0005)\).

Although the mean scores on the HADS of 7.67 \((SD=4.28)\) on the depression subscale and 8.28 \((SD=4.64)\) on the anxiety subscale fall into the doubtful category of anxiety and depression as defined by Zigmond and Snaith\(^ {33} \) it is notable that 32\% of the participants had scores of 11 or higher on the anxiety subscale, indicating definite cases of anxiety, and 21\% had
scores of 11 or higher on the depression subscale indicating definite cases of depression. Scores on the daytime functioning sub-scale of the General Sleep Disturbance Scale ranged from 0 to 19 out of a possible high score of 35. The mean daytime functioning score was 17.75 ($SD = 7.29$), which indicates some limitation in daytime function due to sleepiness every day of the week. Only 35% of the study participants reported feeling alert and energetic during the day on 4 or more days during the week. Feeling sleepy during the day on 4 or more days during the week was reported by 68% of study participants and 45% of study participants reported struggling to stay awake during the day for 4 or more days during the week.

The mean score on the cognitive functioning variable of 27.85 ($SD = 6.81$) out of a possible score of 36 (denoting good cognitive function) indicates difficulty some of the time with forgetfulness, concentrating, and problem solving. In fact 19% of the participants reported having difficulty with problem solving a good bit of the time to all of the time and 8.5% reported having difficulty with concentration or difficulty paying attention a good bit of the time to all of the time. Slow reactions or difficulty with forgetfulness were reported by 11.1% of participants a good bit or all of the time. Confusion a good bit of the time to all of the time was reported by 6% of participants.

Participants experienced a moderate level of interference with activities related to fatigue (mean 30, $SD = 17.59$). When asked to rate their fatigue “right now” on a visual analog scale, 14% of participants reported no fatigue at the time of the survey. However, over half (57%) rated their fatigue “right now” as 5 or higher on a 0-10 visual analogue scale. The usual level of fatigue during the past 24 hours was rated between 3 and 8 by 67% of study participants. This sample of heart failure patients rated fatigue interference with walking (64%), normal work (63%), and general activity (55%) as 5 or higher on a visual analogue scale.
Discomforts of illness. Shortness of breath, edema, and pain are the symptoms included in the discomforts of illness symptom cluster (mean=16.03; SD=8.69). The most highly correlated symptoms in this symptom cluster are shortness of breath and pain ($r = 0.484, p \leq 0.0005$) followed by shortness of breath and edema ($r = 0.426, p \leq 0.0005$) and edema with pain ($r = 0.414, p \leq 0.0005$).

On average, participants experienced moderate limitation associated with shortness of breath (mean=9.23; SD=3.61). While mostly good days or a mix of good and bad days was reported by 90% of the participants, 51% reported moderate to severe shortness of breath over the previous 2 weeks and 68% reported a moderate amount or a great deal of difficulty lying flat without becoming short of breath.

Participants reported a moderate level of peripheral edema (mean=3.91, SD 3.63). Peripheral edema was reported primarily in the feet and ankles (47.9%). Peripheral edema up to the knees was reported by 16.2% of the participants.

In this sample pain caused a moderate level of interference with activities (mean 8.1, SD 6.98). Pain was described as moderate to very severe by 78% of study participants who reported pain and was reported to last more than 2 days by 16% of the individuals reporting pain. Pain interfered at least a moderate amount with normal work for 63% of those who had pain. The sites of pain were lower extremities (41%), chest (37%), back (16%), upper extremities (12%) and abdomen (10%).

GI Distress. The third symptom cluster, GI distress, is composed of appetite, and hunger. On average participants experienced some loss of appetite (mean=6.46, SD=2.74) and hunger (mean=5.01, SD=2.66). Appetite and hunger were moderately correlated ($r = 0.416, p \leq 0.0005$).

In this sample of individuals with heart failure 85% reported decreased appetite and 95%
reported decreased hunger. Among the study participants 32% felt full after eating a small amount of food and 26% said that being short of breath had an effect on the amount of food eaten. The limited variety of foods and the number of pills taken were reported by 20% to have an effect on the amount of food eaten.

There was a moderate correlation between the discomforts of illness symptom cluster and the sickness behavior symptom cluster ($r = 0.661, p \leq 0.0005$). The GI distress symptom cluster did not correlate with either the discomforts of illness symptom cluster ($r = -0.011, p = 0.455$) or the sickness behavior symptom cluster ($r = -0.059, p = 0.272$).

**Regression analysis**

Functional limitations and mobility were outcome variables in the regression analysis. Participants had a moderate amount of functional limitation (mean = 16.10, $SD = 5.09$) and a moderate amount of limitation in mobility (mean = 9.96, $SD = 2.85$). 80% or more of the study participants reported limitation in activities such as walking several blocks, climbing stairs, kneeling or stooping, pushing a vacuum cleaner, and lifting or carrying groceries. Difficulty traveling around the community because of health issues was reported to occur at least some of the time by 27% of study participants and 38% reported spending most days or everyday in the bed or chair because of their health.

The initial model for *functional limitations* included the three symptom clusters, the 3 two-way interaction terms of the symptom clusters, and selected participant characteristics (age, co-morbidity) (See Table 6). Interaction terms were entered into the model to evaluate for cluster independence. Using a backward stepwise elimination model-building approach the model was trimmed of non-significant variables (age, co-morbidity, GI Distress, and the interaction of GI Distress with Discomforts of Illness and Sickness Behavior). This process
resulted in a model incorporating Discomforts of Illness ($\beta = -0.765$, $p = 0.0005$), Sickness Behavior ($\beta = -0.681$, $p = 0.0005$) and the interaction of Sickness Behavior and Discomforts of Illness ($\beta = 0.649$, $p = 0.014$). The interaction between these variables implies that not only do functional limitations increase as discomforts of illness increase, but increases at a faster rate when sickness behaviors are increased. This model explained approximately 58% of the variance in functional limitations ($F = 35.96$, $p = 0.0005$, $R^2 = 0.578$) (See Table 6).

These same variables were entered into a regression model of factors predicting mobility. Variables predictive of mobility include co-morbidity ($\beta = -0.214$, $p = 0.019$) and sickness behavior ($\beta = -0.328$, $p = 0.005$) (See Table 6). A model trimmed of non-significant variables (age, discomforts of illness, GI distress) using the backward stepwise elimination model-building approach, included sickness behavior ($\beta = -0.441$, $p = 0.0005$) and co-morbidity ($\beta = -0.200$, $p = 0.019$) (See Table 6). This suggests that as an individual with heart failure experiences increased sickness behavior symptoms, mobility decreases. This model ($F = 20.68$, $p = 0.0005$, $R^2 = 0.275$) explained almost 30% of the variance in mobility.

**Discussion**

This study examined heart failure symptoms, identified symptom clusters, and evaluated the effect of the identified heart failure symptom clusters on functional limitations and mobility. The incidence of heart failure is high in individuals over 65 years of age$^1$. The mean age of the study sample is 56 years. According to the Centers for Disease Control and Prevention (CDC), the percentage of adults age 45 – 64 years with two or more of nine selected chronic health conditions, which included heart disease and diabetes (a prevalent co-morbidity in our sample) increased during the periods 1999 – 2000 and 2009 – 2012.$^{43}$ Thus, the younger age of our sample is consistent with the younger age reported by the CDC. The individuals in this sample
had decreased cardiac function as indicated by their markedly reduced EF and over half of them required an ICD. While the majority of the study sample was NYHA class II or III, 13% of the sample was NYHA class IV. Patients who have NYHA class IV heart failure are those who have heart failure symptoms at rest and may be difficult to capture as study participants in the outpatient setting. In our participants, these patients were either listed for transplant or were being evaluated for transplant and/or mechanical circulatory support.

The cluster of symptoms (e.g., anxiety, depression, fatigue, daytime function, and cognitive changes) identified in this study, is similar to the constellation of symptoms known as sickness behavior identified by Dantzler\textsuperscript{44} who describes the construct as a highly organized and purposeful response of an organism to activation of the immune system or to non-immune stimuli. Fatigue, depression and changes in daytime functioning due to sleepiness are features of sickness behavior. Kelly et al.\textsuperscript{45} reported that hypersomnia, listlessness, and loss of interest in social activities are features of sickness behavior.

The sickness behavior symptom cluster identified in this study is consistent with but includes additional symptoms than identified by other investigators who studied heart failure symptom clusters.\textsuperscript{22-24} Riegel and Ratcliffe\textsuperscript{22} reported that adults with heart failure who are in NYHA class IV and who present with the group of symptoms known as sickness behaviors have an increased likelihood of being hospitalized or of dying than adults with NYHA class IV heart failure who do not exhibit symptoms associated with sickness behavior. The symptoms that were identified in the sickness behavior cluster included depression, fatigue, and sleepiness. The symptoms in the sickness behavior cluster that we identified empirically using PCA included these three symptoms as well as anxiety and cognitive dysfunction characterized, for example, as forgetfulness, confusion, decreased attention, and concentration.
Few investigators observed symptom clusters which included appetite or hunger. Song, et al.\textsuperscript{26} isolated a symptom cluster that included lack of appetite with lack of energy and difficulty sleeping. In our study appetite and hunger composed a symptom cluster. Diet is a crucial component of effective heart failure management. The association of appetite and hunger with other symptoms in heart failure symptom clusters will need further investigation.

Our approach to the identification of symptom clusters was selection and measurement of individual symptoms prevalent in individuals with heart failure. From this analysis a discomforts of illness symptom cluster composed of dyspnea, pain, and edema emerged. Some of the symptoms in the discomforts of illness cluster (e.g., pain) may receive limited attention by clinicians during the assessment of individuals with heart failure. However, attention to this cluster may be important to helping an individual with heart failure preserve their lifestyle and engage in enjoyable activities.

Investigators have observed relationships between physical functioning and single symptoms--for example fatigue,\textsuperscript{17,19} sleep disordered breathing,\textsuperscript{46,47} pain,\textsuperscript{48} and depression\textsuperscript{20} in individuals with heart failure. However, among the studies examining the relationship of heart failure symptom clusters with outcomes, there are no reports about the relationship between heart failure symptom clusters and functional limitations or mobility. Perhaps the recognition of a need for energy conservation and redirection of activities toward recuperation from an exacerbation of heart failure needs to receive more attention in care planning for individuals experiencing a heart failure exacerbation.

A relationship was observed between the heart failure symptom clusters, sickness behaviors and discomforts of illness with functional limitations. In regression analysis, both increased sickness behaviors and increased discomforts of illness predicted limitations in
functional status. While functional limitations increased as sickness behaviors and discomforts of illness increased, functional limitations increased as a faster rate as sickness behaviors increased. This provides evidence to clinicians that when caring for an individual with heart failure it is important to consider a range of symptoms rather than only the classic heart failure symptoms as sources of functional limitations.

When helping an individual with heart failure improve mobility, addressing sickness behaviors, the strongest predictor of mobility in our study, has the potential to help patients improve functional status. A decrease in sickness behaviors and fewer comorbid conditions is associated with improved mobility which may result in the ability to get out into the community, to use public transportation, and to spend less time spent confined to the bed or chair.

The TUS proved to be an adequate model for the study of heart failure symptom clusters. Three groups of heart failure symptoms that met the definition of a symptom cluster were identified. Although the independence of the symptom clusters sickness behaviors and discomforts of illness with respect to functional limitations may be questionable, we were able to demonstrate that 2 symptom clusters were related to the performance outcome functional limitations and one symptom cluster was related to performance outcome mobility.

**Limitations**

The study findings reported here provide insight into symptom clusters in patients with heart failure; however, we recognize some limitations. First, the findings may not be generalizable because the sample was a convenience sample of heart failure patients followed at one institution. In addition, the sample was composed of symptomatic outpatients followed in a tertiary care setting and the symptom profile of this sample may not be representative of the symptom profile observed in the acute care setting. Study participants could have magnified or
minimized their reporting of symptoms. However, by definition symptoms are an individual’s perceptions which can only be recognized and confirmed by the individual. Instrument selection may have limited the range of symptom characteristics that were considered in developing the symptom clusters identified by this study.

**Implications**

The relationship of the three symptom clusters to functional limitations and mobility outcomes adds to the evidence validating the composition of heart failure symptom clusters. The findings of this study suggest that while it is important to include symptoms such as dyspnea, fatigue, and peripheral edema in heart failure patient assessment it is equally important to inquire about the presence of symptoms such as pain, daytime function, appetite, and hunger. As patients are instructed to manage their heart failure perhaps health care providers need to remember that participation in self-care activities may be limited because the individual with heart failure may suffer from the combination of anxiety, depression, and fatigue which is compounded by daytime dysfunction which includes sleepiness and decreased energy during the day and cognitive dysfunction which includes difficulty with problem solving, forgetfulness and difficulty concentrating.

Several areas for further research are suggested by the findings of this study. More study is needed to establish the stability of heart failure symptom clusters. The finding of an interaction between sickness behaviors and discomforts of illness associated with functional limitations indicates research to confirm the independence of these symptom clusters is warranted. Examination of the relationship of heart failure symptom clusters with biomarkers of heart failure such as the brain naturetic peptide (BNP) may aid the identification of underlying mechanisms producing heart failure symptom clusters. Finally, additional exploration of
associations between symptom clusters and outcomes will advance the science of heart failure symptom cluster identification.

**Summary and Conclusions**

It is early in the evaluation of cluster formation among heart failure symptoms and stability of heart failure symptom clusters across samples and over time has not been established. However, this study lends support for the existence of a cluster of heart failure symptoms similar to those symptoms associated with sickness behaviors as described by Dantzler\(^{44}\) and substantiated by Riegel and Ratcliffe\(^{22}\) in individuals with heart failure. The identification of a symptom cluster composed of symptoms associated with discomfort highlights the significance of illness discomforts such as pain, edema and shortness of breath, in living with heart failure. This finding represents a signal that measures to alleviate symptoms such as pain and shortness of breath need to be prominent in nursing care planning for individuals with heart failure. The relationship of appetite and hunger with other heart failure symptoms has not received much attention by investigators and provides an opportunity for additional research.

Assessment and care for individuals with heart failure should focus on managing a cluster of symptoms which may includes some less typical heart failure symptoms rather than single symptoms. Interventions targeting a cluster of symptoms as opposed to a single symptom can provide a more focused approach to decreasing functional limitations and improving mobility so individuals with heart failure can engage in activities such as moving about the community to do grocery shopping, filling prescriptions, walking, or even sports such as golf.
References


   http://web.ebsochost.com.proxy.library.vcu.edu/ehost/pdfviewer/pdfviewer?sid=b271ab0b-faae-430a-9568-99976fc9ab95%40sessionmgr12&vid=2&hid=25


http://web.ebscohost.com.proxy.library.vcu.edu/ehost/pdfviewer/pdfviewer?sid=45a802e2-e9c3-4dae-85cd-0be4389c6159%40sessionmgr4&vid=2&hid=25. Published May 2, 2008. Updated


http://circ.ahajournals.org/cgi/content/meeting_abstract/124/21_MeetingAbstracts/A8268.


doi:10.1097/JCN.0b013e3181d6de6f


doi:10.1016/j.jpsychores.2009.10.021


doi:10.1097/JCN.0b013e318cfbcbb.


43. Freid VM, Bernstein AB, Bush MA. Multiple chronic conditions among adults aged 45 and over: trends over the past 10 years, NCHS Data Brief No. 100. Atlanta, GA: Centers for Disease Control and Prevention; 2012. http://www.cdc.gov/nchs/data/databrief/db100.pdf


What’s New?

- Three symptom clusters, sickness behavior, discomforts of illness, and GI distress were identified.

- To reduce functional limitations and improve mobility in individuals with heart failure it is necessary to consider symptoms such as anxiety, depression, pain, daytime dysfunction, and cognitive dysfunction.

- Reducing the level of effect by the symptoms in the Sickness Behavior symptom cluster could improve a heart failure patient’s mobility from being bed or chair bound all or most days to only being bed or chair bound some days.
Table 1 Sample Characteristics (N=117)

<table>
<thead>
<tr>
<th>Variable:</th>
<th>f (%)</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td>56 (13)</td>
</tr>
<tr>
<td>20 – 39 years</td>
<td>15 (13%)</td>
<td></td>
</tr>
<tr>
<td>40 – 59 years</td>
<td>49 (42%)</td>
<td></td>
</tr>
<tr>
<td>60 – 79 years</td>
<td>50 (43%)</td>
<td></td>
</tr>
<tr>
<td>≥ 80 years</td>
<td>1 (1%)</td>
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</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>44 (38%)</td>
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</tr>
<tr>
<td>Male</td>
<td>73 (62%)</td>
<td></td>
</tr>
<tr>
<td>Race</td>
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<tr>
<td>White</td>
<td>55 (47%)</td>
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<tr>
<td>African American</td>
<td>59 (50%)</td>
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<tr>
<td>American Indian/Alaska Native</td>
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<tr>
<td>Education</td>
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<tr>
<td>Did not complete high school</td>
<td>20 (17%)</td>
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<tr>
<td>High school graduate</td>
<td>60 (51%)</td>
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</tr>
<tr>
<td>College graduate</td>
<td>37 (32%)</td>
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<tr>
<td>Marital Status</td>
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<tr>
<td>Never married</td>
<td>25 (21%)</td>
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<tr>
<td>Previously married</td>
<td>28 (24%)</td>
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</tr>
<tr>
<td>Currently married</td>
<td>64 (55%)</td>
<td></td>
</tr>
<tr>
<td>Employment Status</td>
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<tr>
<td>Unemployed (but looking for work)</td>
<td>8 (7%)</td>
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<tr>
<td>Employed part time</td>
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<tr>
<td>Employed full time</td>
<td>18 (15%)</td>
<td></td>
</tr>
<tr>
<td>Homemaker</td>
<td>1 (1%)</td>
<td></td>
</tr>
<tr>
<td>Receiving disability</td>
<td>49 (42%)</td>
<td></td>
</tr>
<tr>
<td>Retired</td>
<td>36 (31%)</td>
<td></td>
</tr>
<tr>
<td>Student</td>
<td>1 (1%)</td>
<td></td>
</tr>
<tr>
<td>Volunteer</td>
<td>2 (2%)</td>
<td></td>
</tr>
<tr>
<td>Length of time with heart failure</td>
<td></td>
<td>5.2 (5.3)</td>
</tr>
<tr>
<td>&lt;1 year</td>
<td>15 (14%)</td>
<td></td>
</tr>
<tr>
<td>1– 5 years</td>
<td>51 (48%)</td>
<td></td>
</tr>
<tr>
<td>6 – 10 years</td>
<td>27 (25%)</td>
<td></td>
</tr>
<tr>
<td>11– 15 years</td>
<td>10 (9%)</td>
<td></td>
</tr>
<tr>
<td>&gt;15 years</td>
<td>3 (3%)</td>
<td></td>
</tr>
<tr>
<td>NYHA Classification</td>
<td></td>
<td>2.7 (0.70)</td>
</tr>
<tr>
<td>Class 2</td>
<td>51 (44%)</td>
<td></td>
</tr>
<tr>
<td>Class 3</td>
<td>46 (39%)</td>
<td></td>
</tr>
<tr>
<td>Class 4</td>
<td>15 (13%)</td>
<td></td>
</tr>
<tr>
<td>Ejection Fraction (EF)</td>
<td></td>
<td>25% (10%)</td>
</tr>
</tbody>
</table>

*F* = frequency  
*SD* = standard deviation
<table>
<thead>
<tr>
<th>Symptom</th>
<th>f (%)</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shortness of breath at least once or twice in the past 2 weeks</td>
<td>117 (100%)</td>
<td>3 days (1.8)</td>
</tr>
<tr>
<td>Decreased appetite (9 or less on a visual analogue scale with 0 = no</td>
<td>99(85%)</td>
<td>6.5 (2.7)</td>
</tr>
<tr>
<td>appetite)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased hunger (9 or less on a visual analogue scale with 0 = no</td>
<td>110 (95%)</td>
<td>5 (2.6)</td>
</tr>
<tr>
<td>hunger sensation)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>25 (21%)</td>
<td>7.7 (4.3)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>38 (32.5%)</td>
<td>8.3 (4.6)</td>
</tr>
<tr>
<td>Daytime functioning: Felt sleepy during the day 4 or more days</td>
<td>78(67.8%)</td>
<td>4.5 days (2.4)</td>
</tr>
<tr>
<td>during the week</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue: Felt unusually tired or fatigued in the past week</td>
<td>85 (73%)</td>
<td>0.84 (.89)</td>
</tr>
<tr>
<td>Fatigue: Usual level of fatigue during the past week</td>
<td></td>
<td>4.8 (2.8)</td>
</tr>
<tr>
<td>Edema (1 or greater on a visual analogue scale with 0 = no edema and 10</td>
<td>84 (73%)</td>
<td>3.9(3.6)</td>
</tr>
<tr>
<td>= worst edema I have ever had)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain (1=yes; 0=no)</td>
<td>73 (62%)</td>
<td>3.2 (1.6)</td>
</tr>
<tr>
<td>Cognitive function: Difficulty reasoning and solving problems</td>
<td>49 (42%)</td>
<td>4.7(1.4)</td>
</tr>
<tr>
<td>Cognitive function: Difficulty with concentration and thinking</td>
<td>51(43%)</td>
<td>4.5(1.4)</td>
</tr>
<tr>
<td>at least some of the time</td>
<td></td>
<td></td>
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</table>

*F* = frequency  
*SD* = standard deviation
<table>
<thead>
<tr>
<th>Symptom</th>
<th>Component 1 (Sickness Behavior)</th>
<th>Component 2 (GI Disturbance)</th>
<th>Component 3 (Discomforts of Illness)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shortness of Breath</td>
<td></td>
<td>.758</td>
<td></td>
</tr>
<tr>
<td>Edema</td>
<td></td>
<td>.824</td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td></td>
<td>.737</td>
<td></td>
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<tr>
<td>Anxiety</td>
<td>.832</td>
<td></td>
<td></td>
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<td>Depression</td>
<td>.822</td>
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<td>Daytime Function</td>
<td>.741</td>
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<tr>
<td>Cognitive Function</td>
<td>.761</td>
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<tr>
<td>Fatigue</td>
<td>.757</td>
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<tr>
<td>Appetite</td>
<td></td>
<td></td>
<td>.829</td>
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<tr>
<td>Hunger</td>
<td></td>
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<td>.819</td>
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Table 4: Model Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>Standard Deviation</th>
<th>Minimum Score</th>
<th>Maximum Score</th>
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</thead>
<tbody>
<tr>
<td><strong>Sickness Behaviors</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>• Anxiety</td>
<td>8.28</td>
<td>4.64</td>
<td>0</td>
<td>19</td>
</tr>
<tr>
<td>• Depression</td>
<td>7.67</td>
<td>4.28</td>
<td>0</td>
<td>21</td>
</tr>
<tr>
<td>• Fatigue</td>
<td>30.04</td>
<td>17.59</td>
<td>0</td>
<td>60</td>
</tr>
<tr>
<td>• Daytime Function</td>
<td>17.75</td>
<td>7.29</td>
<td>3</td>
<td>32</td>
</tr>
<tr>
<td>• Cognitive Dysfunction</td>
<td>27.85</td>
<td>6.81</td>
<td>6</td>
<td>36</td>
</tr>
<tr>
<td><strong>Discomforts of Illness</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Shortness of Breath</td>
<td>9.23</td>
<td>3.61</td>
<td>1</td>
<td>15</td>
</tr>
<tr>
<td>• Edema</td>
<td>3.91</td>
<td>3.63</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>• Pain</td>
<td>8.08</td>
<td>6.98</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td><strong>GI Distress</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Appetite</td>
<td>6.46</td>
<td>2.74</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>• Hunger</td>
<td>5.01</td>
<td>2.66</td>
<td>0</td>
<td>10</td>
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<tr>
<td><strong>Participant Characteristics</strong></td>
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<tr>
<td>• Age</td>
<td>56</td>
<td>12.95</td>
<td>20</td>
<td>84</td>
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<td>• Co-morbidity</td>
<td>3.21</td>
<td>1.93</td>
<td>1</td>
<td>11</td>
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<tr>
<td><strong>Outcomes</strong></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>• Functional Limitations</td>
<td>16.10</td>
<td>5.09</td>
<td>10</td>
<td>29</td>
</tr>
<tr>
<td>• Mobility</td>
<td>9.96</td>
<td>2.85</td>
<td>3</td>
<td>13</td>
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</table>
Table 5: Descriptive Statistics of Symptom Clusters

<table>
<thead>
<tr>
<th>Symptom Cluster</th>
<th>Mean</th>
<th>Standard Deviation</th>
<th>Minimum</th>
<th>Maximum</th>
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</thead>
<tbody>
<tr>
<td>Sickness Behaviors</td>
<td>58.89</td>
<td>25.16</td>
<td>11.27</td>
<td>110.50</td>
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<tr>
<td>Discomforts of Illness</td>
<td>16.03</td>
<td>8.69</td>
<td>0.76</td>
<td>33.59</td>
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<tr>
<td>GI Disturbance</td>
<td>9.45</td>
<td>3.75</td>
<td>0.83</td>
<td>16.48</td>
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</table>
Table 6: Regression Analyses of Functional Limitations and Mobility

<table>
<thead>
<tr>
<th>Model:</th>
<th>β</th>
<th>Standard Error</th>
<th>Beta</th>
<th>Significance</th>
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</thead>
<tbody>
<tr>
<td><strong>Functional Limitations</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>(F = 17.68, p = 0.0005, R² = 0.591)</em></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>• Age</td>
<td>0.014</td>
<td>0.029</td>
<td>0.034</td>
<td>0.631</td>
</tr>
<tr>
<td>• Co-morbidity</td>
<td>-0.359</td>
<td>0.188</td>
<td>-0.135</td>
<td>0.059</td>
</tr>
<tr>
<td>• Discomorts of Illness</td>
<td>-0.410</td>
<td>0.164</td>
<td>-0.700</td>
<td>0.014</td>
</tr>
<tr>
<td>• GI Distress</td>
<td>0.192</td>
<td>0.229</td>
<td>0.142</td>
<td>0.404</td>
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<tr>
<td>• Sickness Behavior</td>
<td>-0.139</td>
<td>0.053</td>
<td>-0.687</td>
<td>0.010</td>
</tr>
<tr>
<td>• Sickness Behavior* Illness Discomorts</td>
<td>0.004</td>
<td>0.002</td>
<td>0.645</td>
<td>0.018</td>
</tr>
<tr>
<td>• Sickness Behavior * GI Distress</td>
<td>0.001</td>
<td>0.005</td>
<td>0.071</td>
<td>0.820</td>
</tr>
<tr>
<td>• Illness Discomorts* GI Distress</td>
<td>-0.006</td>
<td>0.013</td>
<td>-0.120</td>
<td>0.662</td>
</tr>
<tr>
<td><strong>Trimmed Model of Functional Limitations</strong></td>
<td><em>(F = 35.96, p = 0.0005, R² = 0.578)</em></td>
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<tr>
<td>• Discomorts of Illness</td>
<td>-0.456</td>
<td>0.106</td>
<td>-0.765</td>
<td>0.0005</td>
</tr>
<tr>
<td>• Sickness Behavior</td>
<td>-0.139</td>
<td>0.031</td>
<td>-0.681</td>
<td>0.0005</td>
</tr>
<tr>
<td>• Sickness Behavior*Illness Discomorts</td>
<td>0.004</td>
<td>0.002</td>
<td>0.649</td>
<td>0.014</td>
</tr>
<tr>
<td><strong>Mobility</strong></td>
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<td></td>
</tr>
<tr>
<td><em>(F = 8.96, p = 0.0005, R² = 0.305)</em></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Age</td>
<td>0.027</td>
<td>0.027</td>
<td>0.089</td>
<td>0.325</td>
</tr>
<tr>
<td>• Co-morbidity</td>
<td>-0.412</td>
<td>0.173</td>
<td>-0.214</td>
<td>0.019</td>
</tr>
<tr>
<td>• Sickness Behavior</td>
<td>-0.048</td>
<td>0.017</td>
<td>-0.328</td>
<td>0.005</td>
</tr>
<tr>
<td>• Discomorts of Illness</td>
<td>-0.064</td>
<td>0.048</td>
<td>-0.151</td>
<td>0.188</td>
</tr>
<tr>
<td>• GI Distress</td>
<td>0.013</td>
<td>0.083</td>
<td>0.013</td>
<td>0.880</td>
</tr>
<tr>
<td><strong>Trimmed Model of Mobility</strong></td>
<td><em>(F = 20.68, p = 0.0005, R² = 0.275)</em></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>• Co-morbidity</td>
<td>-0.388</td>
<td>0.163</td>
<td>-0.200</td>
<td>0.019</td>
</tr>
<tr>
<td>• Sickness Behavior</td>
<td>-0.065</td>
<td>0.012</td>
<td>-0.441</td>
<td>0.0005</td>
</tr>
</tbody>
</table>

*B = unstandardized beta coefficient       Beta – standardized beta coefficient*
Figure 1: Conceptual Framework

**Physiologic Factors**
- NYHA Class
- Ejection Fraction (%)
- Heart Failure
- Etiology
- Co-morbidity
  - Charlson Comorbidity Index

**Psychologic Factors**
- Psychologic
- Fatigue
  - Brief Fatigue Inventory
- Anxiety
  - Hospital Anxiety and Depression Scale
- Depression
  - Hospital Anxiety and Depression Scale
- Peripheral Edema
  - Visual Analogue Scale
- Pain
  - MOS Bodily Pain Scale
- Loss of Appetite
  - Food, Eating Experiences and Diet Questionnaire
- Increased Hunger
  - Food, Eating Experiences and Diet Questionnaire
- Daytime Functioning
  - Daytime Functioning Subscale of the General Sleep Disturbance Scale
- Cognitive Impairment
  - Cognitive Functioning Subscale of the MOS Core Survey

**Symptoms**
- Dyspnea
  - Cardiovascular Limitations & Symptoms Profile
- Fatigue
  - Brief Fatigue Inventory
- Anxiety
  - Hospital Anxiety and Depression Scale
- Depression
  - Hospital Anxiety and Depression Scale
- Peripheral Edema
  - Visual Analogue Scale
- Pain
  - MOS Bodily Pain Scale
- Loss of Appetite
  - Food, Eating Experiences and Diet Questionnaire
- Increased Hunger
  - Food, Eating Experiences and Diet Questionnaire
- Daytime Functioning
  - Daytime Functioning Subscale of the General Sleep Disturbance Scale
- Cognitive Impairment
  - Cognitive Functioning Subscale of the MOS Core Survey

**Performance**
- Functional Limitations
  - Mobility
  - MOS Physical Functioning Measure

---

*Adapted from the Theory of Unpleasant Symptoms (Lenz, Pugh, Milligan & Gift, 1997)
Vita

Janet Kay Herr was born June 13, 1951, in Alton, Illinois and is an American citizen. She graduated from Huguenot High School, Richmond, Virginia in 1969. She received a Bachelor of Science in Nursing from the University of Virginia in 1973. She has been employed as a Registered Nurse at Chippenham Hospital in Richmond, Virginia since graduation from nursing school. Her current position is as a clinical data specialist in quality management. She received a Master of Science in Nursing from Virginia Commonwealth University in 1993 and a Post-master’s Certificate in Aging Studies from Virginia Commonwealth University in 2007.