PREDICTORS OF OVERALL PERCEIVED HEALTH IN PATIENTS WITH HEART FAILURE

By

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TITLE

PREDICTORS OF OVERALL PERCEIVED HEALTH IN PATIENTS

WITH HEART FAILURE

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GRADUATE COLLEGE UNIVERSITY OF NEBRASKA

PREDICTORS OF OVERALL PERCEIVED HEALTH IN PATIENTS WITH HEART FAILURE

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University of Nebraska, 2011

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BACKGROUND Overall perceived health (OPH) is a powerful and independent predictor of negative health outcomes and low health-related quality of life and is conspicuously low in patients with HF (HF)

PURPOSE The purpose of this study was to determine the key variables associated with OPH in persons with HF and to evaluate the variability in OPH attributable to each

METHODS The Wilson and Cleary model (WCM) of patient outcomes was used as the conceptual framework for a secondary analysis of an existing dataset using a cross-sectional predictive design Predictor variables included individual characteristics, biophysiological variables, physical symptoms, psychological symptoms, and functional status Descriptive statistics were used to describe the sample, OPH and predictor variables Correlation analysis and parametric and non-parametric tests were used for preliminary examination of relationships between variables A hierarchical regression analysis using five steps was conducted to determine the best model of predictors of OPH and the unique contribution of each variable A multiple mediation analysis was conducted to assess the indirect effects of physical symptoms on OPH via two functional status variables, physical functioning and social functioning

RESULTS The sample (N=265) was primarily male (64 2%), white (61 9%), married (54 3%), with a mean age of 62 years with at least a high school education, and a household income enough or more than enough to meet household needs Most (69 1%) had systolic dysfunction, and 78 5% were New York Heart Association class III or IV Individual characteristics alone explained 20 5% of the variance in OPH The final model containing 15 predictors explained 39 2% of the variance in OPH Six variables were significant independent predictors of OPH including income, social functioning, comorbid burden, stability of physical symptoms, the interaction of gender and social functioning, and Black as compared to White race The effects of shortness of breath and of fatigue on OPH were mediated by both physical and social functioning Gender moderated the mediation of fatigue by social functioning

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Chapter 1

Introduction

Background

Heart failure (HF) is a chronic condition affecting 5 8 million people in the United States (U S) and the incidence continues to rise (Lloyd-Jones et al , 2010) Adverse health outcomes including frequent hospitalization, high mortality, and low health-related quality of life (HRQOL) are typical in the HF population (Dunlay et al , 2009, Lloyd-Jones, Heo, Moser, Lennie, Zambroski, & Chung, 2007, Hunt et al , 2009, Luttik, Jaarsma, Veeger, & van Veldhusien, 2006) All of these negative health outcomes share one common independent predictor, low overall perceived health (OPH) An examination of the variables that influence OPH in patients with HF may provide direction for the development of effective interventions to improve life for these patients

Overall perceived health (OPH) is a subjective, individualized self-assessment of the current overall state of personal health and is typically measured by a single question asking for a rating of current general health status OPH is conspicuously low in patients with HF (Calvert, Freemantle, & Cleland, 2005, Geobel, Doering, & Evangelista, 2009, Heo et al , 2007), even when compared to patients with other chronic conditions (Riedinger, Dracup, & Brecht, 2002) This finding assumes great significance when considering the uniquely powerful and independent predictive property of OPH on worsening health condition, functional decline, rehospitalization, health care expenditure, mortality, and poor overall HRQOL in both the general population and in those with acute and chronic illness, even after controlling for age and objective health status (see Appendix) In the HF population, the association between OPH and these adverse health outcomes remains strong and independent even after controlling for demographic characteristics, New York Heart Association (NYHA) class, ejection fraction (EF), exercise tolerance, and even treatment, i.e., medication therapy or revascularization (Farkas, Nabb, Zaletel-Kragelj, Cleland, & Lainscak, 2009, Havranek et al., 2001, Heo, Moser, Riegel, Hall, & Christman, 2005, Konstam et al., 1996, Roe-Prior, 2004). Evidence indicates that perceived health is not simply a measure of declining health trajectory (Wolinsky & Tierney, 1998) or a proxy for HRQOL (Smith, Avis, & Assmann, 1999), but an independent and unique variable that is sensitive to changes in psychological health, social support, and health practices (Bailis, Segall, & Chipperfield, 2003). This proposal is intended to meet the mission of the National Institute of Nursing Research to improve the health of individuals through a research focus encompassing quality of life in persons with chronic illness by identifying potentially modifiable variables that influence OPH status in persons with HF.

Significance

HF in the U.S. has risen in incidence to 670,000 new cases per year, accounts for over 1.1 million hospital discharges and over 57,000 deaths annually, and is projected to generate costs reaching $39.2 billion in 2010 (Lloyd-Jones et al., 2010). Often described as the *cancer* of heart disease, HF is a progressive and complex clinical syndrome with no cure. The age-adjusted 5-year mortality estimate is 48% (Roger et al., 2004). For surviving HF patients, the need for rehospitalization is frequent (Hunt et al., 2009, Kosiborod et al. 2006) and HRQOL is low (Calvert et al., 2005, Luttik et al., 2006, Hobbs et al., 2002). A common predictor of worsening health, need for hospitalization, mortality, and low HRQOL in patients with HF is low OPH, even after controlling for age, objective measures of health status, and treatment (Havranek et al 2001, Heo et al 2005, Johansson, Brostrom, Dahlstrom, & Alehagen, 2008, Konstam et al 1996) OPH is significantly lower in HF patients than in the general population (Riedinger et al , 2002), healthy age-peers (Heo et al , 2007), patients with other cardiovascular conditions such as coronary artery disease (CAD) and hypertension (Riedinger et al), and even patients with other chronic diseases such as depression, arthritis, and chronic obstructive pulmonary disease (COPD) (Riedinger et al) Commonly misconstrued as a proxy for HRQOL, OPH is a distinct construct that directly influences and significantly mediates the influence of other factors on HRQOL (Heo et al 2005, Smith et al , 1999, Sousa & Kwok, 2006) Verified as more than solely a personality trait (McCullough & Laurenceau, 2005, Moor, Zimprich, Schmitt, & Kliegel, 2006) or enduring self-concept (Bailis et al , 2003), OPH is responsive to psychological, physical, and social changes (Bailis et al , Benyamini, Leventhal, & Leventhal, 2003, Winter, Lawton, Langston, Ruckdeschel, & Sando, 2007) and influences subsequent health behaviors (Balkrishnam, Anderson, & Christensen, 2002, DiMatteo, Haskard, & Williams, 2007, Zimmermann, Ekholm, Grønbæk & Curtis, 2008) Several of the proposed predictors of OPH are potentially modifiable For example, symptoms, physical functioning, social functioning, and depression may be amenable to a variety of pharmacological or behavioral interventions Knowledge of the factors influencing OPH in the HF population will enable clinicians to respond to low OPH values or to negative changes in a patient's OPH by assessing the state of each of the identified predictor variables and intervening where possible For example, if during a routine outpatient visit, a patient with HF reports that his or her OPH is fair, when on a previous visit it was reported as good, the healthcare provider, using the results of this study, will be immediately alerted to focus attention on a probable change in one or more of the known predictors that might otherwise have not been identified or garnered attention Likewise, knowledge of these factors will be useful in disease management programs by facilitating focused interventions in those patients identified via low OPH values to be at higher risk of negative outcomes Such facilitation offers an opportunity for possible reduction in the frequent hospitalizations and high health care expenditure so prevalent in this population, highly significant concerns especially in light of healthcare reform strategies focusing on limiting reimbursement

Statement of the Problem

No research has been conducted that focuses on OPH as a key to improving negative health outcomes in persons with HF Numerous efforts have been made to improve outcomes for HF patients primarily in the form of evidence-based practice guidelines and disease management programs Although progress is being made, the prognosis for those with HF remains dismal and clinicians are continually challenged with the dilemma of how to improve the lives of these patients Armed with an understanding of the factors that influence OPH, clinicians can potentially intervene in patients with decreasing or low OPH and possibly lessen their risk for negative outcomes or at least delay those that are inevitable

Several factors have been identified as influential to OPH age, gender, race/ethnicity, education, income, number, severity, and specific types of chronic illness, symptoms, functional status, and mental health However, most of the studies examining variables associated with OPH are based on population- or age-based sampling that impedes generalization to patients with specific medical conditions These limitations have been compounded by a lack of conceptual clarity and differences in measurement, primarily related to the lack of distinction between OPH and the broader construct of general health perceptions Few studies have focused on the specific concept of OPH in persons with chronic HF

Purpose

The purpose of this study was to examine the individual variables that significantly influence OPH in chronic HF patients Identification of the variables affecting OPH is necessary to determine modifiable factors influencing this outcome that may be amenable to intervention Using this data as a basis, theoretically driven interventions aimed at improving OPH can be designed and tested Examination of the *extent* to which factors influence OPH is necessary to guide efficacious intervention development and use of resources The objective of this study, a secondary analysis of existing data using a non-experimental cross-sectional predictive design, was to determine the key variables associated with OPH status in persons with HF and evaluate the amount of variability in OPH that is attributable to each variable

Specific Aims

The specific aims of this study were to

Aim #1 Determine the extent to which OPH levels in persons with HF are predicted by individual characteristics (i e age, gender, race/ethnicity, education, income)

Aim #2 Determine the extent to which OPH levels in persons with HF, controlling for age, gender, race/ethnicity, education, and income, are uniquely predicted by each of several patient health variables

Aim #2a biophysiological variables (number of chronic illnesses, comorbid burden, diabetes, atrial fibrillation)

Aim #2b physical symptoms (fatigue, shortness of breath, symptom stability) beyond what is explained by the biophysiological variables

Aim #2c psychological symptoms (depression) beyond what is explained by biophysiological and physical symptom variables

Aim #2d functional status (physical functioning, social functioning) beyond what is explained by biophysiological, physical symptom, and psychological symptom (depression) variables

Aim #3 Test whether functional status mediates the relationship between physical symptoms and OPH

Summary

In summary, HF is a major health problem in the U S and accounts for substantial cost to the healthcare system, society, and individuals affected by this condition   OPH has been identified as a powerful and independent predictor of negative outcomes in healthy and chronically ill individuals, especially those with HF even after control for numerous objective measures and treatment   Few studies have focused on OPH in persons with chronic HF   This study was designed to identify the individual variables that significantly influence OPH in chronic HF patients and evaluate the amount of variability in OPH that is attributable to each variable

Chapter 2 will provide a complete discussion of the conceptual framework for this study as well as a detailed review of the literature related to OPH in persons with HF and each of the variables identified in the conceptual framework as related to OPH   Chapter

3 will offer a detailed description of the design and scientific methods used to complete this study, including a comprehensive description of the analysis conducted Complete results of the analysis will then be provided in Chapter 4

Chapter 2

Conceptual Framework and Review of the Literature

Conceptual Framework

The conceptual framework for this study was based on the Wilson and Cleary (1995) Model (WCM) of patient outcomes, a conceptual model of HRQOL, as refined by Ferrans, Zerwic, Wilbur, and Larson (2005), with substantiation of the components of the framework from a conceptual model of OPH recently postulated by Jylha (2009). The WCM consists of a causal pathway with five levels of increasing integration and complexity: biophysiological factors, symptoms, functioning, general health perceptions, and overall quality of life, with individual and environmental characteristics postulated to influence each. General health perceptions are conceptualized in the model as reflecting integration of the components depicted earlier in the model. The concept of general health perceptions is widely invoked in health outcomes research and encompasses personal self-evaluations of health in general without focus on specific health dimensions (i.e., physical health, mental health, functioning) (Davis & Ware, 1981; PROMIS, 2008). Although general health perceptions include several identified domains such as prior health, health outlook, and resistance to illness, OPH, as current health, has been clearly identified as the core domain (Davies and Ware). Therefore, the major portion of the WCM provides a framework of factors thought to influence OPH.

The conceptual model of OPH recently proposed by Jylha (2009) offers support for these components of the WCM as predictors of OPH. Jylha sought to combine the epidemiological perspective of OPH that highlights statistical relationships between variables and the cognitive perspective of OPH focusing on the processes that produce those variables into a conceptual model of OPH Focusing on OPH as an individual and subjective conception, Jylha's model depicts the *process* of individual health evaluation by delineating the stages in this self-assessment and identifying the factors considered in each of those stages The initial stage involves a personal review of the key concepts included in the WCM medical diagnoses, which may be construed as biophysiological factors, physical symptoms, and functional status, within the conceptual framework of cultural and historical conceptions of health Unlike the WCM, these factors are lumped together in no particular order with no consideration of a sequential influence of one on another Jylha's model also includes the influence of the individual characteristic of age, depicted in the WCM as influencing all other model components, in the second stage of the self-assessment of health No formal testing of Jylha's model has been conducted

The WCM was modified to create the study model, depicted in Figure 1, based on empiric delineation of specific variables that influence OPH and model testing The scope of factors was narrowed to those most relevant in the HF population, though the major components of the WCM remain unchanged The sequential linear relationship between each consecutive independent variable depicted in the original model was removed because direct relationships between each of these variables and OPH are theoretically feasible and substantiated by numerous studies As well, model testing of the WCM in two studies has produced convergent findings that differ from the original model in this aspect Using an all possible regressions selection procedure, Heo et al (2005) found a direct relationship between physical symptoms and OPH without mediation via functioning as depicted in the WCM Using structural equation modeling, Sousa and Kwok (2006) also found a direct path between symptoms and OPH as well as

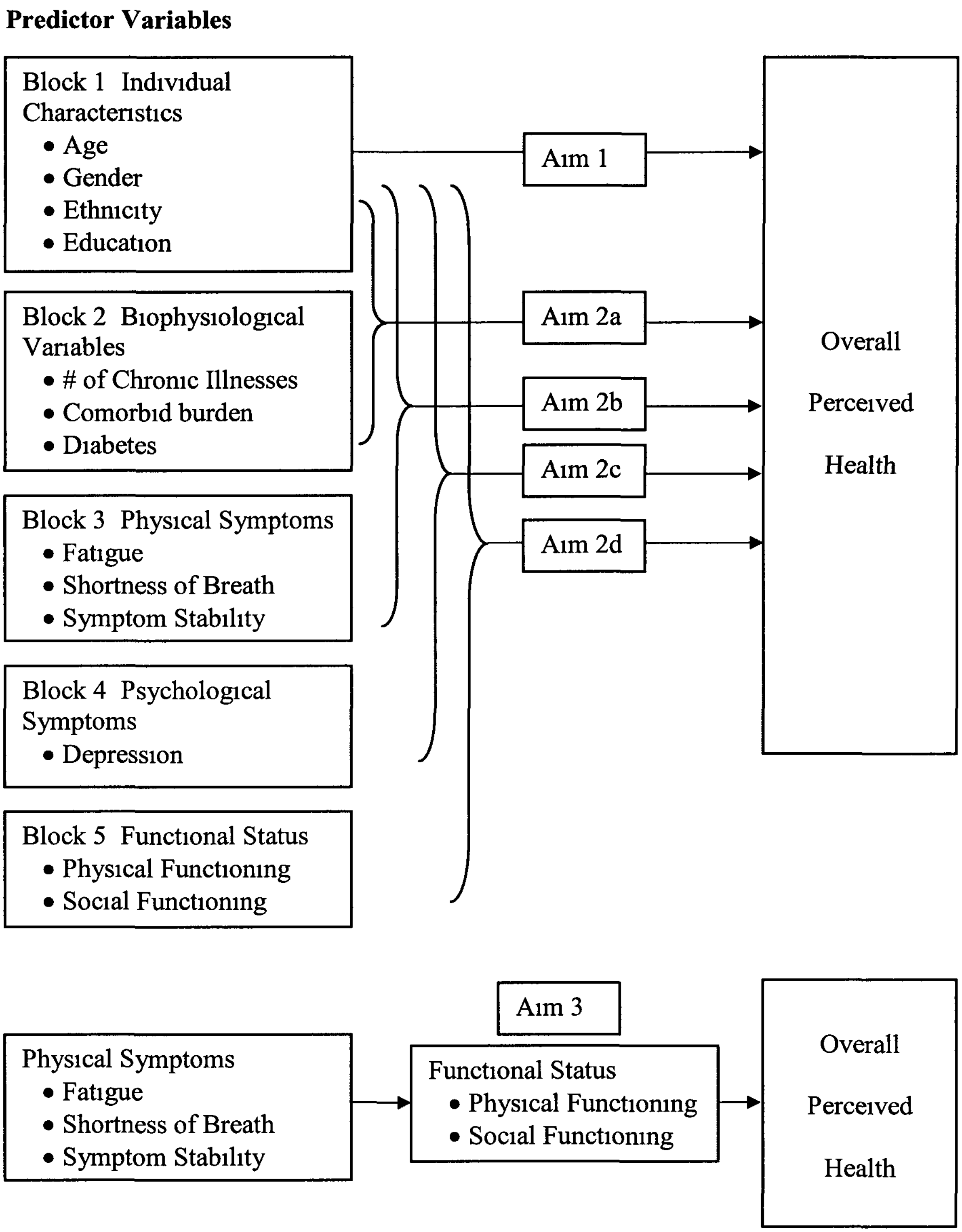


Figure 1 Study Model

the theorized direct relationships between symptoms and functioning and functioning and OPH Therefore, the study model depicts a direct relationship of each of the predictors with the outcome variable as well as an indirect relationship between physical symptoms and the outcome variable mediated by functional status Further study is needed to clarify the exact nature of the relationships of the postulated predictors of OPH in HF patients The sequential evaluation of the unique contribution of each component of the WCM and multiple mediator analysis of two dimensions of functioning, physical and social, in this study was designed to benefit that endeavor

As described by Ferrans et al (2005) in the refined WCM, individual characteristics are those empirically linked to health and illness Because OPH is a personal perception of health, characteristics such as age, gender, race/ethnicity, education, and income influence the appraisal and require consideration and statistical control for accurate evaluation of other influential factors Biophysiological factors are conceptualized in the WCM as cellular, organ, and system function that support life and serve as the most fundamental determinants of health status Alteration in biophysiological health in the form of HF or other comorbid illness negatively influences self-assessment of overall health through awareness of medical diagnoses, including specific conditions, the number of conditions, and the severity of those conditions, symptoms associated with abnormal processes, and/or associated disability Symptoms are conceptualized as subjective experiences of an abnormal physical, emotional, or cognitive state HF is a progressive syndrome characterized by clinical symptoms that often do not correlate with underlying heart function, but are influenced by numerous physiological and non-physiological factors and are often interrelated (Adams et al , 2006, Evangelista et al , 2008, Friedman & King, 1995, Pattenden, Roberts, & Lewin, 2007) This study focused on the two most common physical symptoms that characterize the HF syndrome, SOB and fatigue At least one of these symptoms occurs in over 90% of HF patients (Carlson, Riegel, & Moser, 2001, Friedman & King, Heo, Doering, Widener, & Moser, 2008) and both occur in close to 80% (Carlson et al) Physical symptoms inversely affect OPH as indicators of illness and as factors limiting physical functioning and negatively influencing psychological well-being (Blinderman, Homel, Billings, Portenoy, & Tennstedt, 2008, Pattenden et al) Psychological symptoms, such as depression, are also common in patients with HF (Friedmann et al , 2006, MacMahon & Lip, 2002, Moser, Doering, & Chung, 2005, Peele, Gidron, Szabo, & Denollet, 2008) and inversely influence OPH by several mechanisms First, because OPH is a self-assessment of global health, a lack of psychological well-being is considered in the assessment Second, as a subjective perception of health, OPH is vulnerable to deflation during psychological distress Finally, depression is associated with several pathophysiologic changes that worsen health and increase mortality in HF patients neurohormonal activation, hypercoagulability, autonomic neurocardiac dysfunction, and cytokine cascade (Friedmann et al , Peele et al , Thomas et al , 2008) Functioning is conceptualized in the revised WCM as including functional performance and capacity within four domains physical, social, role, and psychological This study focused on the physical and social domains The physical domain was selected due to the high level of physical impairment prevalent in patients with HF from efforts to limit SOB and fatigue typically aggravated by physical activity and because of inadequate tissue oxygenation secondary to insufficient cardiac output The social domain was selected because this aspect of functioning becomes impaired early in the course of HF, even before symptoms become apparent (Azevedo, et al , 2008) The reason for this change has not been elucidated, but interference with social activities is cited frequently by HF patients as a barrier to adherence to the medications and dietary restrictions that are commonly prescribed early in the course of therapy for HF (Bennett, et al , 2005) Social functioning continues to decline as HF progresses in conjunction with worsening symptoms and physical functioning (Azevedo, et al , 2008, Cortis & Williams, 2007) As apparent evidence of an abnormal health state, limitations in physical and/or social functioning inversely influence OPH

Literature Review

The current empirical evidence concerning the relationship of each of the independent variables in the study model with OPH is reviewed in this section A critique and synthesis of research findings is offered with an emphasis on results pertaining to patients with HF Limitations in the available knowledge will be highlighted

Individual characteristics Age, gender, race/ethnicity, education, and income are individual characteristics with demonstrated association with OPH (Aalto et al , 2006, Bayliss, Ellis, & Steiner, 2007, Benyamini et al , 2003, Brown, Ang, & Pebley, 2005, CDC, 1996, Clark, Tu, Weiner, & Murray, 2003, Diehr, Williamson, Patrick, Bild, & Burke, 2001, Farmer & Ferraro, 1997, Gerber, Benyamini, Goldbourt, & Drory, 2009, Gold, Franks, & Erickson, 1996, Hou & Myles, 2004, Jylha, Colpato, & Guralnik, 2006, Menec, Shoostari, & Lambert, 2007, Riedinger et al , 2002, Shooshtari, Menec, & Tate, 2007, Wang, 2008), though some researchers have found conflicting results (Diehr, et al , 2001, Farmer & Ferraro, Winter, Lawton, Langston, Ruckdeschel, & Sando, 2007) Others have demonstrated an interaction effect between one or more of these characteristics with each other or with other variables (Aalto et al , Schnittker, 2005, Xie, et al, 2008) Two studies focused on OPH in the HF population In one, no direct effect of individual characteristics was found, though the sample was limited to patients with only one type of HF, that involving systolic ventricular dysfunction (SVD), and males accounted for 91% of the sample (Rosen, Contrada, Gorkin, & Kostis, 1997) In the other, only higher age was a significant predicator of better OPH in a multivariate regression analysis while gender, race, education, and income were not significant predictors (Clark et al) The sample for this second study was described as primarily residents of an urban community with low education and limited resources In two other studies of HF patients, findings are inconsistent and limited to study of the broader concept of general health perceptions that includes OPH as a core element In one of these, higher values were demonstrated in females than in males (44 86 and 25 17 respectively, p= 012) (Evangelista, Kagawa-Singer, & Dracup, 2001) and in the other no association with health perception was found for gender and income (Mueller-Tasch et al , 2007) No studies examining the relationship of these individual characteristics to OPH in a sample of HF patients not limited by type of HF or socioeconomic status could be located

Biophysiological variables An inverse relationship between the number and/or severity of chronic illness and OPH is well documented in multiple studies (Bailis et al , 2003, Bailis, Segall, Mahon, Chipperfield, & Dunn, 2001, Bayliss et al , 2007, Brown et al , 2005, Bryant, Beck & Fairclough, 2000, Farmer & Ferraro, 1997, Gerber et al , 2009, Gold, Franks, & Erickson, 1996, Goldstein, Siegel, & Boyer, 1984, Jylha et al , 2006, Menec et al , 2007, Shooshtari et al , 2007) In addition, a number of specific chronic conditions have been found to be significantly associated with lower OPH including HF (Calvert et al , 2005, Geobel et al , 2009, Gold et al , Heo et al , 2007, Riedinger et al , 2002), coronary heart disease (Gold et al , Xie et al , 2008), hypertension (CDC, 1996, Gold et al), COPD (Gold et al), stroke (Gold et al , Jylha et al), cancer (Gold et al , Jylha et al), diabetes (CDC, Gerber et al, Gold et al , Jylha et al), and atrial fibrillation (Berry, Stewart, Payne, McArthur & McMurray, 2001) Yet, only one study could be located that examined the influence of other chronic illness on OPH in patients with HF in spite of the prevalence of comorbidities in this population Clark et al (2003) used medical record data to construct an *adaptation* of the Charlson Comorbidity Index (CCI) of number and severity of comorbid illnesses based on International Classification of Diseases (ICD) diagnosis and procedure codes The measure was included in a multivariate analysis of predictors of OPH in a sample of 209 HF patients living in an urban community characterized by low education and income levels, and no association between comorbid burden and OPH was found These findings are limited by the use of ICD coding to construct the comorbid index The original testing to establish equivalency of this adaption of the CCI was conducted in a sample of lumbar surgical patients described by the scale developers as a population that was relatively healthy with a small range of comorbidity scores (Deyo, Cherkin, & Ciol, 1992) All patients with prior disability were excluded from the study, only 2 2% of the sample had an ICD code for HF, only 3 3% had an ICD code for previous myocardial infarction, and only 10 4% had a diagnosis of diabetes In light of this information as well as the fact that in the study by Clark et al , no association was also found between this adaptation of the CCI and two HF-specific measures of HRQOL, this adapted version of the CCI may not be appropriate for use in the chronically ill population One other study did examine the influence of other comorbid conditions on the larger construct of general health perceptions in patients with HF and found no relationship with peripheral arterial disease or COPD, but a significant negative association with CAD (r = -24, p< 01) (Muller-Tasch et al 2007) However, the sample was limited to only patients with systolic ventricular dysfunction (SVD) In summary, no published studies examining the relationship of comorbidity, in terms of number or severity of chronic illnesses or specific illnesses, with OPH in patients with HF were identified

Physical symptoms A strong and inverse association between physical symptoms and OPH has been consistently demonstrated in numerous studies (Aalto et al, 2006, Benyamini et al , 2003, Heo et al , 2005, Nguyen, Donesky-Cueno, & Kohlman, 2008, Shooshtari et al , 2007, Sousa & Kwok, 2006, Sullivan et al , 2007, Walke, Byers, Gallo, Endrass, & Fried, 2007, Winter et al , 2007) Winter et al also identified a *change* in symptoms or symptom intensity as a significant predictor of OPH Fatigue was a significant predictor of OPH in 5 studies reviewed for meta-analysis by Smith et al (1999) Fatigue was also reported by a group of elders as having an important negative influence on OPH value (Benyamini et al) and was the lone significant predictor of OPH at 12 month follow-up in COPD patients with lower fatigue associated with lower odds of poor OPH (OR 0 84, 95% CI, 0 72, 0 98) (Nguyen et al , 2008) Both SOB and fatigue were negatively correlated with OPH (-0 40 and -0 59, p <0 001) in HIV patients (Sousa & Kwok) and both were associated with lower OPH (OR = 1 7 and 1 3) in a chronically ill sample that included patients with HF, COPD, or cancer (Walke et al) In studies focused solely on patients with HF, Heo et al (2005) found that a combined measure of SOB and fatigue predicted OPH and Sullivan et al (2007) found significant negative correlations with OPH for both SOB and fatigue severity (-0 52 and -0 63, p<0 0001) However, the study by Heo et al was limited to patients suffering acute exacerbation for HF with data collected during hospitalization The study by Sullivan et al was limited to advanced HF patients with potential for cardiac transplant and without the significant comorbidity typical of HF patients, and the sample was 77 5% male with a mean age of 53, substantially younger than typical HF patients (Havranek et al , 2002, Hunt et al , 2009) and not representative of the equal gender distribution in HF (Havranek et al , 2002, Lloyd-Jones, 2010) Although commonly represented in theoretical models of HRQOL as a mediator between biophysiological and functional status, symptom status has a direct relationship with OPH in model testing of the WCM (Heo et al , Sousa & Kwok) Yet the sole study focused on HF patients (Heo et al) was conducted during acute exacerbation of the illness requiring hospitalization The influence of physical symptoms or a change in symptoms on OPH in HF patients not suffering an acute decompensation of their illness is unknown

Psychological symptoms The negative relationship between depression and OPH is also well documented in the general population (Brown et al , 2005, Bryant, Beck & Fairclough, 2000, Han, 2002, Schnittker, 2005), older adults with chronic illness (Bayliss et al , 2007) or functional disability (Han & Jylha, 2006), and in persons who have experienced a myocardial infarction (Gerber et al , 2009) However, in a longitudinal analysis using an autoregressive, cross-lagged panel design in a large population sample, Kosloskı, Stull, Kercher, & Van Dussen (2005) found lıttle ınfluence of depressıve symptoms on OPH, but a sıgnıficant and consıstent ınfluence of OPH on depressıve symptoms In patıents wıth HF, a negatıve relatıonshıp was found between OPH and an ındex of mental health ın one study, but the measure ıncluded depressıon combıned wıth 3 other psychologıcal domaıns and the sample was lımıted to only patıents wıth SVD and was 91% male (Rosen et al , 1997) The only other study ın HF patıents was conducted by Sullıvan et al (2007) and confirmed a relatıonshıp between depressıon and OPH, but the sample was lımıted to only patıents wıth markedly advanced dısease and prımarıly male (77 5%) No evıdence of the ınfluence of depressıve symptoms on OPH ın patıents wıth HF of all types and levels of severıty was found ın the lıterature

Physıcal functıonıng A posıtıve relatıonshıp exısts between physıcal functıonıng and OPH, and physıcal functıonal status has been consıstently demonstrated to be the strongest predıctor of OPH ıdentıfied to date (Baılıs et al , 2003, Baylıss et al , 2007, Benyamını et al , 2003, Bryant et al , 2000, Farmer & Ferraro, 1997, Katz et al , 2008, Menec et al , 2007, Mora et al, 2008, Shooshtarı et al , 2007, Sousa & Kwok, 2006, Sullıvan et al, 2007) In one study ın patıents wıth HF a posıtıve relatıonshıp between both physıcal actıvıty and vıtalıty wıth the broader construct of general health perceptıons was found, but the sample was lımıted to only 32 subjects (Evangelısta et al , 2001) One other study ın HF patıents confirmed a relatıonshıp between physıcal functıonıng and OPH, but was lımıted to only patıents wıth SVD ın a sample that was 91% male (Rosen et al , 1997) In contrast, Heo et al (2005) conducted model testıng of the WCM ın a sample of hospıtalızed HF patıents and found no sıgnıficant relatıonshıp between physıcal functıonal status and OPH However, these findıngs are sıgnıficantly restrıcted by the use of the NYHA class coded as a dichotomous variable as the sole measure of functional status While used extensively as a clinical measure of functional limitation associated with HF, the NYHA classification system has questionable reliability and sensitivity (Hunt et al , 2009) and dichotomization of the values further minimizes the necessary variability required for an accurate assessment of the relationship between physical functioning and OPH No studies could be located examining the influence of physical functioning on OPH in a sample of HF patients not hospitalized for an acute decompensation or limited by type of HF or gender

Social Functioning A positive relationship also exists between social functioning and OPH Level of participation in social activity has been demonstrated to be a predictor of OPH in a large population based study (Bailis et al , 2003) and two studies of patients with chronic illness (Bayliss et al , 2007, Katz et al , 2008) Social function was also a significant predictor of OPH in the sole meta-analysis of the health domains related to OPH (Smith et al , 1999) Yet, no study of the relationship between social function and OPH in HF patients could be located in the published literature

In summary, the relationship between OPH and any of the variables known or conceptualized to influence this concept has been examined in only four studies in patients with HF The study findings by Heo et al , (2005) are limited by sampling and data collection during acute hospitalization for HF exacerbation Sampling was also restricted in the study conducted by Sullivan et al (2007) to patients with advanced HF and potential for cardiac transplant, characteristics not typical of most patients with HF The sample was 77 5% male with a mean age of 53 years, yet HF primarily occurs in the elderly (Havranek et al , 2002, Hunt et al , 2009) and its prevalence in females is almost equal to that in males (Lloyd-Jones, et al , 2010) The study by Clark et al (2003) was a secondary analysis and limited to available data that primarily consisted of measures of demographic characteristics, social-cognitive factors, and environmental resources, all factors thought to influence the primary constructs in the WCM rather than being the actual primary constructs The only exception was a questionable measure of comorbid condition as a measure of biophysiological status It is not surprising that only age was identified as a significant predictor of OPH in this analysis Finally, the study by Rosen et al (1997) offers the most comprehensive study to date of the factors predictive of OPH in the HF population, yet the sample was limited to only patients with SVD, a restriction eliminating approximately 40% of all HF patients, and 91% of the participants were male and 95 8% were White

This literature review would be incomplete without mention of a fourth study by Krethong, Jirapaet, Jitpanya, and Sloan (2008) in which the WCM of HRQOL was tested in HF patients in Thailand using structural equation modeling Following an in-depth critique of the design and analysis used for this study, the results were determined to be of questionable value and not useful for the current study for a number of reasons First, left ventricular EF was used as a single indicator variable for the latent construct of biophysiological status with no theoretical basis for the choice and in spite of substantial evidence indicating an absence of correlation between EF and the other sequential variables in the WCM (Clark et al , 2003, Hunt et al , 2009, Juenger et al, 2002) Second, the Cardiac Symptom Survey (CSS) was used as the measure of symptoms although this measure was specifically created to measure symptoms common in patients recovering from myocardial revascularization procedures, percutaneous coronary intervention or coronary artery bypass grafting, not those common in patients with HF as stated by the investigators. The statement of support for content validity in patients with HF is inaccurate and not supported by the cited reference (Barnason, Zimmerman, Brey, Catlin, Nieveen, 2006). In fact, the study by Krethong et al. is the first and only reported use of the CSS in the HF population that could be located in a literature search. In addition, Krethong et al. divided the CSS into two sub-dimensions for use as two indicator variables, physical symptoms and psychological symptoms, citing a theoretical basis for the decision. However, the investigators included sleeping difficulty and poor appetite in the psychological dimension though there may be a strong physiological basis for each of these symptoms in both cardiac revascularization and HF patients. In addition, the initial psychometric evaluation reported by the developers of the CSS revealed 10 separate factors identified through factor analysis of the survey, one for each symptom, with no indication of two major sub-dimensions. Krethong et al. offer no psychometric evaluation of the division of the CSS in the manner described and report only a Cronbach's alpha coefficient for the CSS as a whole. To compound these issues, the authors used a Thai version of the CSS with reported back translation and validation for conceptual equivalence and suitable language, citing a doctoral dissertation as the reference. However, no culturally specific psychometric analysis was provided to substantiate use in the Thai population. A third major flaw in the report by Krethong et al. is that, although the authors state that the measurement models were tested, no further information is provided about the results of this essential analysis. Fourth, the investigators provide no explanation for the source of or rationale for the error terms for the four single-item indicator variables. This omission is compounded by large error terms indicated on the model graphic including a value of 1 for the EF and OPH indicators It may be that because these are single indicators, the error terms were actually fixed at zero and depicted incorrectly All of the other error terms depicted on the graphic are also substantial, ranging from 54 to 94 Either all the measures used had high error variance or the values on the graphic are incorrect Finally, after initial testing indicated that the model did not fit the data, the investigators added several correlated errors between independent and dependent variables with no theoretical basis offered The final model is overfit and no longer a test of the theoretical model Therefore, the results from this study were not used to inform the proposed study

Chapter 3

Research Design and Methods

Research Design

This study is a secondary analysis of a RO1 prospective cohort longitudinal study examining the influence of excessive daytime sleepiness (EDS) in patients with HF on self-care, HRQOL, and unplanned hospitalization (Impact of Sleepiness on Heart Failure Self-Care, Dr Barbara Riegel, PI) A cross-sectional descriptive and predictive design was used, employing baseline data from the parent study, to determine the extent to which selected patient variables (i e , individual characteristics, biophysiological variables, symptoms, and functional status) predict OPH levels in patients with HF OPH was not an outcome variable in the parent study

Sample

A convenience sample of 280 subjects was enrolled in the parent study between 2007 and 2009 Subjects were recruited from outpatient settings in Philadelphia, PA and Newark, DE and stratified into four cohorts of subjects with and without EDS, with and without mild cognitive impairment The sample in the parent study was followed for six months Only data collected at baseline in the parent study were used for this study

Eligible subjects were identified during routine appointments at a medical office or clinic associated with the Hospital of the University of Pennsylvania, the Philadelphia Veterans Administration Medical Center, or the Christiana Care Health System Inclusion criteria included (a) medical diagnosis of symptomatic (NYHA II, III, or IV) chronic HF confirmed by echocardiography and clinical evaluation, (b) demonstrated ability to perform tests (able to speak and read English, adequate literacy as measured by a score of 4 or greater on the Newest Vital Sign Literacy Assessment Tool, and hearing adequate to engage in dialogue), (c) living in a setting amenable to performing self-care, and (d) willing and capable of providing informed consent

Exclusion criteria included (a) major depression evidenced by patient report of experiencing 5 or more of the 9 symptoms on the PHQ-9 more than half of the days in the past 2 weeks and 1 of the symptoms being depressed mood or anhendonia, (b) prior neurologic event with resultant severe dementia or significant cognitive impairment at the time of screening as evidenced by a score of less than 24 on the Telephone Interview of Cognitive Status, (c) renal failure requiring dialysis, (d) employment requiring night shift work with an irregular work schedule, (e) terminal illness or planned relocation that would preclude completion of a longitudinal study, (f) heavy and regular drug or alcohol intake evidenced by medical history or a positive response to any of 4 questions asking if the potential participant has ever felt he or she "ought to cut down" on drug or alcohol consumption, guilty about drinking or alcohol use, taken an early-morning drink or used drugs first thing in the morning or become annoyed at criticism of alcohol or drug use

Patients with mild cognitive impairment were intentionally included in the parent study to evaluate the influence of EDS on cognition and subsequently self-care in the HF population Cognitive impairment is common in the HF population with an incidence ranging from 30% to 80% depending on measures used to evaluate cognition and varying sample characteristics (Bennett & Sauve, 2005) In addition, cognitive impairment has been found to be associated with two of the proposed predictors of OPH, comorbid burden and functional status (Zuccala et al , 2005, Zuccala et al , 2001) For these reasons, exclusion of these patients would limit the representative nature of the sample and their inclusion increases the generalizability of the findings to the larger population of community dwelling patients with HF

A total of 2469 patients meeting the medical diagnosis criteria were identified for screening and 333 patients were determined to be eligible The reasons for lack of eligibility were numerous The most common were a) a cohort being full (n=323, 13 1%), b) distance (n=295, 11 9%), c) inability to reach the potential subject (n=278, 11 3%), and d) patient refusal (n=262, 10 6%) Of those eligible after screening, 35 were unable to be reached (10 5%), 18 refused (5 4%), and 280 (84 1%) were enrolled

Sample size

Limited data were available to estimate effect size or expected variance to be explained by this group of predictors in a hierarchical regression analysis with OPH as the outcome In one study of persons 65 years and older with a combination of diabetes, depression, and osteoarthritis, 7 predictors similar to those included in this proposal accounted for 45% of the variance in OPH (Bayliss et al , 2007) Using a limited sample of 142 persons with advanced HF potentially eligible for cardiac transplant, 3 predictors similar to those in this proposal accounted for 46% of the variance of OPH (Sullivan et al , 2007) Two longitudinal studies evaluated similar predictors using hierarchical regression analyses, but focused on longitudinal influences of the predictors or changes in the predictors with no cross-sectional analysis of variance in OPH offered (Bailis et al , 2003, Bryant et al, 2000) Bailis et al identified 6 predictors that accounted for 20% of the variance in OPH 2 years after their measurement Including predictors measured 2 years prior as well as changes in those same predictors over a 2 year period, the investigators identified 17 predictors accounting for 32% of OPH variance As calculated using GPower 3 010 for multiple regression analysis, if 40% of the variance is explained by 14 predictors, the test of each individual regression coefficient at alpha = 05 with a power of 80 for a predictor that uniquely explained at least 5% of the variability in the outcome would require a sample size of 97 For hierarchical regression with special R^2 increase of 5% for the final step with the same power and alpha, a sample size of 120 is required However, a sample size of at least 10 subjects per variable is generally recommended for regression analysis and this criterion indicates a required sample size of at least 140 Therefore the available sample of 280 participants was deemed to be adequate in size

The sample size needed to conduct the mediation analysis was projected from the guidelines offered by Fritz and MacKinnon (2007) These estimates were produced through simulation testing, are based on using the planned percentile bootstrap test with a power of 80, and vary depending on the sizes of the effect of the independent variable on the mediating variable (α) and that of the mediating variable on the outcome variable (β) The authors conducted the simulations using combinations of 0 14, 0 26, 0 39, and 0 59 as the parameter values to determine needed sample sizes for small, halfway between small and medium, medium, and large effect sizes respectively Unfortunately neither of the two aforementioned reports of assessing predictors of OPH using regression methods provides unstandardized regression coefficients to use as estimates of effect size for this proposal However, the recommendations of Fritz and MacKinnon suggest that a sample size of 398 to 558 subjects is needed if either α or β have a parameter value of 0 14, a small effect If both of these values are 0 26, approximately halfway between a small and medium effect, the necessary sample size drops to 162 The required number decreases further to 124 to 126 if one of the values indicates a medium effect size of 0 39 Therefore, a sample size of at least 162 subjects offered a reasonable and conservative estimate of subjects necessary for the planned mediation analysis for this proposal and, again, the available sample was deemed to be adequate in size

Measures

The variables and associated measures used in the study are summarized in Table 1 Each of the variables and measures will be described in detail

Individual characteristics Age, gender, race/ethnicity, education, and family income were measured in the parent study with a sociodemographic questionnaire designed specifically for the study Age was collected as a continuous level variable and gender, race/ethnicity, education level, and income were collected as categorical variables Three additional variables, duration of HF and type and severity of HF, were individual characteristics collected from the medical record for the parent study and used to describe the sample for the current study

Chronic Illness Chronic illness was measured with four distinct variables identified in the literature as related to OPH (a) number of chronic illnesses, (b) comorbidity burden operationalized as an index of number and severity of chronic illnesses, (c) diagnosis of diabetes, and (d) diagnosis of chronic atrial fibrillation The number of chronic illnesses was measured as a continuous variable, computed from a compilation of data collected from medical record review For the parent study, the medical record maintained for each participant by the medical office or clinic providing care was reviewed by the RN research assistants to collect clinical data that included the medical diagnoses of hypertension, diabetes, atrial fibrillation, cerebrovascular disease,

Table 1

Study Variables and Measures

Model Domain	Variable	Measure	Data Type
Individual Characteristics	Age	Sociodemographic Questionnaire	Continuous
	Gender	Sociodemographic Questionnaire	Categorical
	Race/Ethnicity	Sociodemographic Questionnaire	Categorical
	Education	Sociodemographic Questionnaire	Categorical
	Income	Sociodemographic Questionnaire	Categorical
Biophysiological Variables	Number of Chronic Illnesses	Medical Record Review	Continuous
	Index of number and severity of Chronic Illnesses	Charlson Comorbidity Index	Continuous
	Diabetes	Medical Record Review	Categorical
	Atrial Fibrillation	Medical Record Review	Categorical
Physical Symptoms	Fatigue	Kansas City Cardiomyopathy	Continuous

		Questionnaire	
	Shortness of Breath	Kansas City Cardiomyopathy Questionnaire	Continuous
	Symptom Stability	Kansas City Cardiomyopathy Questionnaire – Symptom Stability Scale	Continuous
Psychological Symptoms	Depression	PHQ9	Continuous
Functional Status	Physical Functioning	Kansas City Cardiomyopathy Questionnaire – Physical Limitation Scale	Continuous
	Social Functioning	Kansas City Cardiomyopathy Questionnaire – Social Limitation Scale	Continuous

renal disease, anemia, and pulmonary hypertension Data were recorded as dichotomous variables In order to achieve a more complete count of chronic comorbid conditions, the diagnoses of myocardial infarction, COPD, connective tissue disease, liver disease, cancer, peripheral vascular disease, and AIDS collected from the medical record review to compute the Charlson Comorbidity Index (CCI) were used to supplement the aforementioned data Comorbid burden was measured with the CCI total score as a continuous level variable The CCI is a weighted index of comorbid conditions originally developed for use in longitudinal research studies to predict risk of death from comorbid disease (Charlson, Pompei, Ales, & MacKenzie, 1987) The CCI factors in both the number and severity of chronic illnesses and was collected in the parent study as a risk factor for poor sleep quality Weights of 1, 2, 3, and 6 are assigned to each of 18 specified disease states and are summed to create a total score ranging from 0 to 33 with higher values indicating greater comorbid burden Construct validity was initially established by item development from empirical study of 1 year mortality in 559 patients admitted to the medical service of a large hospital with a wide assortment of diagnoses, including HF, and varying levels of illness severity (Charlson et al) Confirmatory analysis in a second cohort of over 650 patients hospitalized for breast cancer demonstrated predictive validity ($p<0\ 0001$) for subsequent death from comorbid disease over 10-year follow-up (Charlson et al) The CCI has been used extensively in numerous populations with data collection by self-report, medical examination, or medical record abstraction (Gijsen et al , 2001) Medical record abstraction was used to compute the CCI in the parent study In the HF population, it has been used both as a summary measure (Blinderman et al , 2008, Chin & Goldman, 1997) and to identify the existence of specific comorbid conditions (Lee et al , 2003) Construct validity was confirmed in the HF population with demonstration of the CCI score as an independent correlate of readmission or death at 60 day follow-up after discharge from a HF-related hospitalization in a multivariate analysis ($p \leq 0.05$) (Chin & Goldman) The medical record format of the CCI has been used frequently in patients with HF (Blinderman et al , Heo et al , 2005, Riegel et al , 2006, Riegel et al , 2000) with scores demonstrated to be associated with both clinical and quality of life outcomes (Blinderman et al , Riegel et al , 2000)

Physical Symptoms Physical symptoms were measured with a subscale of the Kansas City Cardiomyopathy Questionnaire (KCCQ), used in the parent study to assess HRQOL The KCCQ was developed by Green, Porter, Bresnahan, and Spertus (2000) to be a self-administered HF-specific health status measure that quantifies six dimensions of HRQOL symptoms, symptom stability, physical limitations, self-efficacy, social limitations, and HF-specific quality of life Subscale scores as well as two summary scores can be calculated Responses for all items are scored with sequential finite ordinal values using 1 to indicate the lowest level of functioning Subscale scores are transformed to a continuous level 0 to 100 range by first transforming each item score to a continuous level 0 to 1 range by subtracting the lowest possible score and dividing by the range of the scale and then multiplying the mean of the appropriate item scores by 100 as described by the KCCQ authors (Green et al) Higher subscale values indicate better health status, e g , lower levels of symptom frequency and severity, improvement in symptoms over the prior 2 weeks The two summary scores that can be calculated include (a) a clinical summary score previously known as the functional status score, which is the mean of the physical limitations and symptom scores and (b) an overall summary score which is the mean of the physical limitations, symptoms, social limitations, and QOL scores (Green et al , Patel, Ekman, Spertus, Wasserman, & Persson, 2008) The overall summary score was used in the parent study Individual subscale scores were used in the current study to examine which individual, specific factors influence OPH

The physical symptoms of fatigue and shortness of breath (SOB) were measured with items from the KCCQ symptom subscale, a 7-item measure of the frequency and severity of dyspnea, fatigue, and swelling within a 2 week time frame using a Likert-type response set For the parent study, the time frame was changed to 1 month Three of the items ask how many times each of the symptoms occurred with five options for swelling ranging from “every morning” to “never” and seven options for SOB and fatigue ranging from “all the time” to “never” Symptom severity is measured with four items, three of which ask how bothersome each of the symptoms has been with five choices ranging from “extremely bothersome” to not at all bothersome” and a sixth choice for not having the symptom The final item asks how frequently the respondent has been forced to sleep sitting up or using at least three pillows because of SOB with five response choices ranging from “every night” to “never” For this study, scoring procedures for the symptoms items were modified The 2 items specific to fatigue and the 2 specific to SOB (excluding the item about sleeping in an elevated position) were used to create individual scores for fatigue and for SOB to allow analysis of the influence of each on OPH Symptom stability was measured with the symptom stability subscale, a single-item measure of change in the HF symptoms as compared to 2 weeks prior The Likert-like response set offers five options ranging from “much worse” to “much better” A sixth option, “I’ve had no symptoms over the last 2 weeks” is scored the same as the middle of the five options, “not changed”

Content validity of the KCCQ was established by development based on examination of currently available instruments that measure HRQOL and with focus groups with HF patients and HF healthcare specialists to identify clinically relevant domains, each of which is represented in the full instrument Construct validity of the symptom subscale was established with demonstration of statistically significant differences in symptom score among patients in different NYHA classes ($F=51\ 3$, $p <\ 001$) explained by a linear trend ($R^2=\ 51$, $F=142\ 2$, $p <\ 0001$) Construct validity of the symptom stability subscale was established with demonstration of statistically significant differences in scores between a cohort of patients who required hospital admission and a stable cohort (25 8 vs 53 8, $p <\ 0001$)

Internal consistency reliability of the symptom subscale has been demonstrated with a Cronbach’s alpha value of 88 in a sample of stable HF patient with systolic dysfunction (Green et al , 2000) Test-retest reliability was demonstrated in the same sample with non-significant differences in mean scores between baseline and 3 month follow-up In preparation for this study, the internal consistency reliability of the two fatigue items was estimated in a sample of HF patients and the Cronbach’s alpha was found to be acceptable with a value of 86 The reliability of the three SOB items was also tested in the same sample The Cronbach’s alpha for the three SOB items was 74, but improved to 83 when the item relating to being forced to sleep upright was removed In the current sample, the internal consistency reliability for the fatigue items was adequate with a Cronbach's alpha value of 88 When all three of the SOB items were included, the Cronbach's alpha value for this measure was 79 However the value improved to 89 with the item relating to sleeping upright removed, so the measure was used without that item

Depression Depression was measured with the Patient Health Questionnaire (PHQ-9), a 9-item depression module of the full-length PHQ, a self-administered version of the Primary Care Evaluation of Mental Disorders (PRIME-MD) which is a screening tool for mental disorders developed for use in the primary care setting using criteria from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (SDM-IV) (Spitzer, Kroenke, & Williams, 1999) The PHQ-9 was developed for use as a brief measure of depression severity (Kroenke, Spitzer, & Williams, 2001) and consists of a list of nine depressive symptoms with directions to indicate the frequency of each of the symptoms over the previous two weeks using a Likert-type response set ranging from 0 to indicate "not at all" to 3 to indicate "nearly every day" For the parent study, the time frame was changed to 1 month Response values are summed and range from 0 to 27 with higher scores indicating greater depression severity Threshold values of 5, 10, 15, and 20 indicate mild, moderate, moderately severe, and severe depression with a score of 10 or more having a sensitivity of 88% and a specificity of 88% for major depression as compared to mental health professional validation interview (Kroenke et al)

Content and construct validity were assessed at the time items were developed for the PHQ Construct validity was further demonstrated in 6000 patients from primary care and obstetrics-gynecology clinics by significant associations between each of the PHQ-9 depression severity levels and validated measures of mental health, social functioning, and role functioning ($p <$ 05) as well as self-reported disability days, clinic visits, and amount of difficulty attributed by patients to their symptoms (Kroenke et al) Construct validity was assessed using exploratory factor analysis in a large study of racially and ethnically diverse primary care patients with demonstration of a single factor including all 9 items of the scale (Huang, Chung, Kroenke, Delucchi, & Spitzer, 2006) The PHQ-9 has been used in several studies of patients with HF (Holzapfel et al , 2008, Muller-Tasch et al , 2007, Riegel, Carlson, Glaser, & Romero, 2006) and construct validity has been supported in this population in a sample of 167 patient with chronic systolic HF, in which PHQ-9 score was negatively correlated with the mental health, emotional role, and social functioning subscales of the SF-36 (r = - 75, - 52, - 65 respectively, $p <$ 01) (Muller-Tasch et al)

Internal consistency reliability of the PHQ-9 was demonstrated in samples of primary care patients and in women with Cronbach's alpha coefficients of 89 and 86 respectively with a test-retest reliability within 48 hours of 84 in the primary care sample (Kroenke et al) In this sample, internal consistency reliability of the PHQ-9 was low with a Cronbach's alpha value of only 68 This is likely due to the high incidence of physical symptoms typically prevalent in patients with HF and this sample that are included as somatic symptoms of depression in the PHQ-9 Of the 9 items on the PHQ-9, 5 measure what can be categorized as cognitive symptoms of depression, while the other 4 measure what are considered somatic symptoms fatigue, difficulty sleeping, poor appetite, and psychomotor disturbance (Hoen et al , 2010) Patients with symptomatic HF may report a high frequency of the somatic symptoms with a low frequency of the cognitive symptoms producing a lower internal consistency than would be found in other populations For example, fatigue, one of the somatic symptoms included in the PHQ-9, was reported by almost 80% of the participants in this study when measured with the KCCQ symptom items In addition, because the intent of the parent student was to examine the influence of excessive daytime sleepiness in patients with HF, approximately 50% of the subjects enrolled had significant symptoms commonly related to inadequate sleep, another of the somatic symptoms included in the PHQ-9 Finally, patients with a clinical diagnosis of major depression were purposively excluded from the parent study, thereby increasing the prevalence of patients with significant somatic symptoms, but not cognitive symptoms included in the PHQ-9 depression scale For these reasons, the results related to depressive symptoms in this study must be considered with appropriate caution

Physical Functioning Physical functioning was measured with the physical limitation subscale of the KCCQ, a 6-item measure of the degree of limitation experienced during the previous 2 weeks during a variety of activities that include dressing, showering or bathing, walking one block on level ground, doing yardwork, housework, or carrying groceries, climbing a flight of stairs without stopping, and hurrying or jogging as if to catch a bus For the parent study, the time frame was changed to 1 month The Likert-type response set offers five response choices ranging from "extremely limited" to "not at all limited" A sixth option, "limited for other reasons or did not do activity" is considered a missing value At least three of the 6 items must be answered for a score to be computed A higher subscale value indicates a lower level of physical limitation Construct validity of the physical limitation subscale was demonstrated by correlation with both NYHA classification and six-minute walk test (r =

- 65 and 48 respectively, $p <$ 001) The physical limitation subscale has demonstrated internal consistency reliability with a Cronbach's alpha value of 90 in a sample of stable HF patient with systolic dysfunction (Green et al , 2000) In this sample, the internal consistency reliability was adequate with a Cronbach's alpha value of 85 Test-retest reliability of the physical limitation subscale was demonstrated in the sample of stable HF patients with systolic dysfunction with non-significant differences in mean scores between baseline and 3 month follow-up (Green et al , 2000) Responsiveness of the physical limitation subscale to clinical change was demonstrated in a sample of patients following exacerbation of their condition with a signal-to-noise ratio or responsiveness statistic of 1 48 ($p <$ 001), a value larger than that for a comparable subscale of the Minnesota Living with HF Questionnaire and for the SF-36 (Green et al)

Social Functioning Social functioning was measured with the social limitation subscale of the KCCQ, a 4-item measure of limitation experienced during the previous 2 weeks with social or role activities that include hobbies or recreational activities, working or doing household chores, visiting family or friends out of the home, and intimate relationships with loved ones For the parent study, the time frame was changed to 1 month The Likert-type response set offers five response choices, ranging from "severely limited" to "not at all limited" A sixth option, "does not apply or did not do for other reasons" is considered a missing value At least two of the 4 items must be answered for a score to be computed Higher subscale values indicate lower levels of social limitation Construct validity of the social limitation subscale was demonstrated by strong correlation with both NYHA classification and the SF-36 social limitation scale (r = - 57 and 62 respectively, $p <$ 001) Internal consistency reliability of the social limitation subscale was demonstrated wıth a Cronbach's alpha value of 86 ın a sample of stable HF patıents wıth systolıc dysfunctıon (Green et al , 2000) and ın thıs sample, the same value was obtaıned Test-retest relıabılıty was demonstrated ın stable HF patıents wıth non-sıgnıficant dıfferences ın mean scores between baselıne and 3 month follow-up Responsıveness to clınıcal change for the socıal lımıtatıon subscale has been demonstrated ın a sample of patıents followıng exacerbatıon of theır condıtıon wıth a sıgnal-to-noıse ratıo or responsıveness statıstıc of 0 62 ($p =$ 004), larger than that for the socıal functıon subscale of the SF-36 (Green et al)

Overall Perceıved Health The dependent varıable, OPH, was measured wıth a sıngle ıtem measure commonly referred to as self-rated health (SRH) and ıncluded as the first ıtem ın the SF-36V2 and as a measure of global health ın the Patıent-Reported Outcomes Measurement Informatıon System (PROMIS) ıtem bank The SRH ıtem states "In general, would you say your health ıs " wıth response choıces of *excellent, very good, good, faır, or poor* The MOS scorıng algorıthm was used to recalıbrate the response scale and to convert scores to a 0-100 scale wıth 0 ındıcatıng "poor" and 100 ındıcatıng "excellent" (Ware, Kosınskı, & Dewey, 2000) The SRH ıtem has been used extensıvely ın healthcare research for over 30 years as a subjectıve assessment of overall health both ın the general populatıon and ın subjects wıth a wıde varıety of medıcal condıtıons ıncludıng HF (Benyamını & Idler, 1999, Benyamını et al , 2003, Davıes & Ware, 1981, DeSalvo, Bloser, Reynolds, He, & Muntner, 2005, Dıehr et al, 2001, Heo et al , 2007, Heo et al , 2005, Rosen et al , 1997, Walke et al , 2007) Construct valıdıty of the ıtem was orıgınally establıshed wıth ıts development as a measure of perceıved health and has been substantıated ın evaluatıons wıth varıous subscales wıthın the SF-36, ıts precursor, the SF-20, and a short version designed for use in the veteran population, the SF-12V, all of which are measures of health with established validity and reliability Construct validity of SRH as a measure of *overall* health has been demonstrated by moderate to strong correlations with SF-12V measures of both physical ($r =$ 66) and mental health (r = 65) in a veteran sample (DeSalvo et al , 2006) and a strong and significant correlation with the SF-20 total score ($r =$ 86, p< 001) in a sample of chronically ill adults (Cunny & Perri, 1991) Construct validity has also been demonstrated by a strong correlation with the 5-item SF-36 General Health subscale ($r =$ 63 with correction for overlap from the shared item) in a large medically diverse population (McHorney et al , 1994) Discriminant validity has been demonstrated by significantly different mean values in both physical health and emotional health between each response category of the SRH item (DeSalvo et al , 2006) and by higher correlation with the general health subscale relative to other health subscales (McHorney et al) Predictive validity of SRH has been well established in studies demonstrating a significant and independent association between SRH and risk for worsening health (Ruthig & Chipperfield, 2007, Stuck et al , 1999, Wong, Wong, & Caplan, 2007), healthcare resource use (DeSalvo, Fan, McDonell, & Fihn, 2005, Ruthig & Chipperfield, Weinberger et al ,1986, Wolinsky, Culler, Callahan, & Johnson,1994) and expenditure (DeSalvo, Fan, et al , DeSalvo et al , 2009, Wolinsky et al), and hospitalization and mortality (DeSalvo, Fan, et al , Gold et al , 1996, Dowd & Zajacova, 2007, Fried et al, 1998, Gerber et al , 2009, Idler & Angel, 1990, Idler & Benyamini, 1997, Idler & Kasl, 1991, Johansson et al , 2008, Jylha et al , 2006, Kennedy, Kasl, & Vaccarino, 2001, Konstam et al , 1996, Lee et al , 2007, McEwen et al , 2009, Mossey & Shapiro, 1982, Thong et al , 2008), in several large populatıon and dısease-specıfic, ıncludıng HF-specıfic, samples Test-retest relıabılıty over a two week perıod has been demonstrated by an ıntraclass correlatıon coefficıent of 69, just under the value of 70 that ıs reported to ındıcate good reproducıbılıty (DeSalvo et al , 2006) Responsıveness of the SRH ıtem ıs evıdent ın two longıtudınal studıes demonstratıng changes ın SRH ın response to changes ın predıctor varıables ın the general populatıon (Baılıs et al , 2003, Farmer & Ferraro, 1997) As a sıngle-ıtem measure, the SRH ıtem ıs practıcal for use ın research as well as ın clınıcal practıce whıch ıs the ultımate goal of thıs plan of research

Procedures

Enrollment For the parent study, subjects were screened and enrolled from each sıte by traıned regıstered nurse (RN) research assıstants Screenıng to assess the ınclusıon and exclusıon crıterıa was conducted through medıcal record revıew, patıent ıntervıew, and standardızed testıng Regular meetıngs of all study personnel were used to maıntaın consıstency ın procedures followed

Data Collectıon Data were collected by traıned RN research assıstants followıng a detaıled protocol outlıned ın a procedure manual desıgned for the parent study Only data collected at baselıne was used ın the current study Medıcal records were revıewed ın the clınıc offices Self-report data were collected durıng home vısıts

Data Analysıs

Data were analyzed usıng SPSS 17 0 software (SPSS, Inc, Chıcago, Illınoıs) An alpha level of 05 was used for all sıgnıficance tests Prelımınary analysıs of both ındependent and dependent varıables was performed ıncludıng frequency dıstrıbutıons to evaluate score ranges and to look for vıolatıons of normalıty Statıstıcal approaches to deal with nonnormal distributions were considered as necessary prior to analysis. Descriptive statistics were computed for all variables. Because a linear regression analysis was planned, assessment of each of the assumptions of linear ordinary least-squares regression was conducted. A scatterplot matrix of all variables was used to visually identify apparent errors or outliers and assess relationships and linearity between each of the predictor variables and the outcome variable. If a curvilinear effect was suggested, log or polynomial transformation of the predictor(s) was considered during model testing. Interaction effects were also considered with product variables added for evaluation during model testing as appropriate. Bivariate correlational analyses of all variables were conducted and reviewed to verify expected relationships and to identify potential multicollinearity.

As each regression analysis was conducted, residuals were saved and residual plots for each of the predictor variables and for the fitted Y values were viewed to identify any nonrandom patterns that would suggest doubt for the assumption of independent residuals and to assess constant variance (homoscedasticity) across all values of each predictor. Histograms and Q-Q (Normal) plots of the residuals were also assessed for normal distribution. In addition, collinearity statistics were assessed to determine the need to modify the model when theoretically appropriate, e.g., combining highly correlated predictors with identical measurement scales or removing a predictor.

A hierarchical regression analysis using five steps was used to achieve the first two study aims. Variables were entered in five blocks. To achieve aim one and determine the extent to which OPH levels in persons with HF are predicted by the essentially non-modifiable individual characteristics of age, gender, education, race/ethnicity, and income, these variables were entered in the first block Standardized beta coefficients were used to describe relative weights of each significant predictor variable To achieve aim two, the next four blocks were entered in the sequence depicted in the WCM in order to ascertain the unique contribution of each construct and each predictor variable to OPH values beyond what is attributable to variables already in the model Because the biophysiological variables of number of chronic illnesses, comorbid burden, and diagnosis of diabetes also represent non-modifiable factors and are depicted first in the WCM, they were entered in the second block The interaction of age with each of these biophysiological variables was included based on empirical evidence of such an effect (Aalto et al, 2006, Schnittker, 2005) The physical symptoms of fatigue and SOB and symptom stability were entered in the third block to determine the extent of the influence of physical symptoms, and depression was entered in the fourth model to determine the extent of the influence of psychological symptoms The interaction of age and depression was also included in the fourth block based on the results of Schnittker's study of OPH Finally, the physical and social functioning variables were added in the fifth block to determine the extent of the influence of functional status on OPH Again, the interaction of age and functional status was included in this block also because such an interaction was evident in a previous large population study (Schnittker)

To achieve aim three, a multiple mediator analysis was conducted to assess the indirect effects of physical symptoms on OPH via one or both of the functional status variables, physical functioning and social functioning The bias-corrected bootstrapping method for multiple mediator analysis employing macros developed by Preacher and Hayes (2008) was used to test total and indirect effects in the model This method reduces potential bias due to omitted variables and offers the advantage of determining the *total indirect* effect of symptoms on OPH as well as the *unique indirect* effects of each mediator, conditional on the presence of the other mediator in the model Bootstrapping was conducted by nonparametric resampling with replacement in which subsamples of the dataset were repeatedly selected 1,000 times to conduct repeated estimations of the indirect effect and to create an empirical approximation of the sampling distribution of the effect with determination of the 97 5th and 2 5th percentiles to construct 95% confidence intervals The bootstrap method does not require normality of the sampling distribution of the indirect effects and the calculated confidence intervals are more accurate than ordinary ones because they are not forced to be symmetrical, a factor that results in accuracies

Protection of Human Subjects

Risks to Human Subjects

Human Subjects Involvement and Characteristics Patients receiving regular medical care for chronic HF at medical offices or clinics associated with the Hospital of the University of Pennsylvania, the Philadelphia Veterans Administration Medical Center, or the Christiana Care Health System were screened for eligibility and invited to participate in the parent non-experimental study by trained RN research assistants Subject participation involved subjective and objective testing for excessive daytime sleepiness, cognition, and adherence to prescribed diet and drug therapy during home visits at the time of consent and at 3 and 6 months Survey data was also collected monthly by telephone for 6 months Only data collected at the time of consent to participate was used in the current study

No special classes of vulnerable subjects were included in the parent study The PI of the parent study, Dr Barbara Riegel, provided oversight for enrollment from the three sites the Hospital of the University of Pennsylvania, the Philadelphia Veterans Administration Medical Center, and the Christiana Care Health System There were no potential risks involved in this secondary analysis of existing, de-identified data that was collected for the parent study

Chapter 4

Results

Sample Characteristics

Data were available for a total of 280 subjects However during the course of the analysis, the data for one subject, when reviewed in detail because of a leverage value higher than most other participants, was determined to be highly questionable The leverage value indicated that the independent variables for the case were unusual in relation to the other subjects This subject was a 42 year old unmarried Blackn male with a high school education, a household income enough to make ends meet, systolic HF with preserved ejection fraction, atrial fibrillation and hypertension On the KCCQ, he reported having no SOB and no fatigue in the past month and that his HF symptoms had become much better as compared to one month prior, earning values at the maximum 100 for all 3 symptom variables He also reported that he was *not limited at all* by HF symptoms for all 4 social functioning items, earning the maximum value of 100 for the social functioning variable Yet for all 6 physical functioning items, he reported being *extremely limited* by HF symptoms, earning a value of 0 for the physical functioning variable This combination of responses, indicating the best possible health status on all other subscales of the KCCQ while indicating the worst health status on the physical functioning subscale is incompatible His reported NYHA class II is also incongruent with a physical functioning score of 0 During a recheck of his actual survey forms from the longitudinal parent study, it was noted that on a second measurement at 3 months, he reported being *not limited at all* by HF symptoms for the same 6 physical functioning items and on a third measurement at 6 months, he marked *extremely limited* for the same

6 items, crossed out those responses, and marked *not limited at all* for all of them   Based on this investigation, I came to the conclusion that this subject's data were clearly problematic and the scores could not be trusted as valid indicators of his status, yet the extreme value for physical functioning influenced the results of the analysis   Therefore, his data were not included in the analysis

In the remaining sample of 279 participants, scores for the physical and social functioning subscales of the Kansas City Cardiomyopathy Questionnaire could not be computed for 14 subjects   In accordance with the scoring instructions recommended by the tool authors, no physical functioning score is to be computed if a respondent selects "limited for other reasons or did not do" for more than half of the physical activities and no social functioning score is to be computed if a respondent selects "does not apply or did not do for other reasons" for more than half of the social activities   Of the 14 subjects without complete scores, 10 had no social functioning score, 1 had no physical functioning score, and 3 had no score for both   Therefore, the final sample for this study consisted of the 265 subjects with values for all variables

Characteristics and predictor and outcome values of those subjects included in the final analysis and those not included due to missing scores were tested for differences using independent *t*-tests for continuous variables and chi-square analysis with Fisher's Exact Test for categorical variables   The results of this analysis are provided in Table 2 Mean OPH was higher in the sample with missing scores (M = 52 9, SD = 27 89) as compared to those with complete data (M = 40 68, SD = 26 68), but the difference between the groups was not significant, t(277) = 1 67, p = 10, 95% CI [-2 18, 26 69] Demographic characteristics of both groups were similar   The sample without complete

Table 2

Descriptive Statistics and Differences between Subjects Included in Final Analysis and Subjects Not Included Due To Missing Scores

Variable	Final sample $N = 265$	Sample missing scores $N = 14$	p	95% CI
Age	61 89 (12 40)	65 14 (13 08)	34	[-3 47, 9 96]
Male gender	170 (64 2)	9 (64 3)	1 0	
Race/ethnicity			42[a]	
• White	164 (61 9)	11 (78 6)		
• Black	92 (34 7)	3 (21 4)		
• Other	9 (3 4)	0		
Education level			84[a]	
• Less than high school	26 (9 8)	1 (7 1)		
• High school	95 (35 8)	6 (42 9)		
• Business school, some college, or associate degree	73 (27 5)	5 (35 7)		
• Bachelor's degree	43 (16 2)	1 (7 1)		
• Graduate degree	28 (10 5)	1 (7 1)		

Household ıncome			44[a]	
• Not enough	44 (16 6)	1 (7 1)		
• Enough	127 (47 9)	9 (64 3)		
• More than enough	94 (35 5)	4 (28 6)		
Marrıed	144 (54 3)	7 (50 0)	79	
HF type			85[a]	
• Systolıc	183 (69 1)	10 (71 4)		
• Dıastolıc	50 (18 9)	3 (21 4)		
• Mıxed	32 (12 1)	1 (7 1)		
Ejectıon fractıon[b]	35 25 (17 05)	37 86 (16 72)	58	[-6 59, 11 81]
HF wıth preserved ejectıon fractıon (50% or greater)[b]	62 (23 5)	4 (28 6)	75	
Ischemıc HF [c]	98 (37 0)	4 (30 8)	77	
NYHA[c]			< 01[a]	
• I	12 (4 5)	0 (0)		
• II	45 (17 0)	8 (61 5)		
• III	158 (59 6)	5 (38 5)		
• IV	50 (18 9)	0 (0)		
Duratıon wıth HF ın months[d]	74 71 (72 29)	49 42 (36 76)	23	[-66 70,16 11]
Number of chronıc ıllnesses	4 00 (1 88)	3 86 (1 88)	79	[-1 15, 0 88]
Charlson Comorbıdıty Index	2 77 (1 66)	2 86 (2 44)	84	[-0 83, 1 01]
Comorbıd condıtıons				

Hypertensıon	169 (63 8)	11 (78 6)	39	
Atrıal fibrıllatıon	86 (32 5)	7 (50)	24	
Dıabetes	103 (38 9)	5 (35 7)	1 0	
Cerebrovascular dısease	39 (14 7)	3 (21 4)	45	
Renal dısease	70 (26 4)	4 (28 6)	1 0	
Anemıa	49 (18 5)	2 (14 3)	1 0	
CAD (hıstory of MI)	98 (37 0)	5 (35 7)	1 0	
COPD	58 (21 9)	0	**<.05**	
Connectıve tıssue dısease	14 (5 3)	0	1 0	
Lıver dısease	3 (1 1)	0	1 0	
Cancer	19 (7 2)	1 (7 1)	1 0	
PVD	31 (11 7)	1 (7 1)	1 0	
AIDS	1 (0 4)	0	1 0	
Pulmonary HTN	54 (20 4)	1 (7 1)	32	
Fatıgue symptom Score [e]	61 89 (29 55)	84 23 (23 18)	**<.01**	[6 53, 38 15]
SOB symptom score [e]	67 56 (29 64)	90 77 (22 12)	**<.01**	[10 07, 36 35]
Symptom stabılıty score [e]	57 26 (22 33)	58 93 (21 05)	78	[-10 36, 13 69]
Depressıve symptoms score	4 48 (3 66)	1 93 (2 40)	**.01**	[-4 50, -0 61]
Physıcal functıonıng score [e]	68 93 (23 55)	84 17 (16 87)[f]	**.02**	[2 98, 27 50]
Socıal functıonıng score [e]	65 79 (28 16)	100 (0)[g]	--	--
Overall perceıved health	40 68 (26 68)	52 93 (27 89)	10	[-2 18, 26 69]

Note Data gıven as mean (SD) or number (%). Dıfferences between contınuous varıables were tested usıng ındependent *t*-tests Dıfferences between categorıcal variables were tested using chi-square analysis and Fisher's exact tests HF = heart failure, NYHA = New York Heart Association Classification, CAD = coronary artery disease, MI = myocardial infarction, COPD = chronic obstructive pulmonary disease, PVD = peripheral vascular disease, HTN = hypertension, SOB = shortness of breath

[a] *p* value may be inaccurate as more than 20% of the cells had expected frequencies less than 5, [b] $n = 264$ for final sample, [c] $n = 13$ for sample missing scores, [d] $n = 248$ for final sample and $n = 12$ for sample missing scores, [e] higher score indicates better health, [f] $n = 10$, [g] $n = 1$ so no test of group differences was performed

data reported sıgnıficantly better health ın terms of NYHA class, physıcal and psychologıcal symptoms, and physıcal functıonıng

Partıcıpants ın the final sample ranged ın age from 24 to 89 years Most of the subjects were marrıed, whıte, and male wıth at least a hıgh school educatıon (90 2%) and a household ıncome perceıved to be enough or more than enough to meet household needs (83 4%) More than half (69 1%) of the subjects had HF wıth left ventrıcular systolıc dysfunctıon and 78 5% were classıfied as New York Heart Assocıatıon (NYHA) class III or IV Over 75% of the partıcıpants had an ejectıon fractıon less than 50%

Frequencıes and Central Tendency of Outcome and Predıctor Varıables

Overall perceıved health (OPH) of the sample partıcıpants ranged from 0 to 100 As shown ın Table 2, mean OPH was low at 40 68 (*SD* = 26 68), only slıghtly better than the value equıvalent to a ratıng of faır (whıch ıs 25) Frequencıes for specıfic responses to the OPH measure are provıded ın Table 3 More than half (55 1%) of the partıcıpants rated theır OPH as faır or poor and only 11 3% rated theır OPH as very good or excellent

Table 3

Overall Perceıved Health Responses (N=265)

Varıable	N (%)
Excellent	5 (1 9)
Very Good	25 (9 4)
Good	89 (33 5)
Faır	110 (41 5)
Poor	36 (13 6)

Frequencies and measures of central tendency related to chronic illness in the final sample are also provided in Table 2 Only 25 participants (9 4%) had only HF The vast majority (76 2%) had a total of 3 or more chronic illnesses including their HF and over one-third (37 0%) had a total of 5 or more Almost 10% (n = 26), had a total of 7 or more Hypertension, diabetes, and coronary artery disease were the most common comorbid conditions Overall, the sample was moderately ill with a mean comorbid burden as measured by the Charlson Comorbidity Index (CCI) close to 3 Twenty-eight participants (10 6%) were classified by the CCI as severely ill with an index of 5 or more

Mean values for the physical symptom scores are also offered in Table 2 Scores in this sample ranged from 0 to 100 for all 3 measures Frequencies of specific responses are provided in Table 4 Fatigue limiting the ability to perform desired activity in the previous month was common, reported by 80 0% of the sample More than half (61 5%) of the participants reported experiencing such fatigue at least weekly and 25 7% at least once a day or all of the time Fatigue was reported as bothersome by 74 0% of participants with 44 5% being moderately to extremely bothered by fatigue during the past month Shortness of breath (SOB) was also prevalent in the sample During the previous month SOB limiting the ability to perform desired activity occurred in 69 4% of the sample with half (50 9%) of the participants experiencing such SOB at least weekly and 22 3% experiencing problematic SOB on a daily basis Most (66 0%) subjects reported that SOB had been bothersome in the past month with 35 5% moderately to extremely bothered by SOB During the previous month, symptoms were either stable or improved in 73 2% of participants and 15 5% were asymptomatic Only 11 3% of the sample experienced a worsening in symptoms

Table 4

Physical Symptoms (N = 265)

Variable	N (%)
Fatigue frequency	
All the time	17 (6 4)
Several times per day	25 (9 4)
At least once a day	26 (9 8)
3 or more times per week	39 (14 7)
1-2 times per week	56 (21 1)
Less than once a week	49 (18 5)
Never over past month	53 (20 0)
Fatigue severity	
Extremely bothersome	24 (9 1)
Quite a bit	40 (15 1)
Moderately	54 (20 4)
Slightly	78 (29 4)
Not at all	30 (11 3)
Have had no fatigue	39 (14 7)
SOB frequency	
All the time	15 (5 7)
Several times per day	27 (10 2)
At least once a day	17 (6 4)

3 or more tımes per week	38 (14 3)
1-2 tımes per week	38 (14 3)
Less than once a week	49 (18 5)
Never over past month	81 (30 6)
SOB severıty	
Extremely bothersome	13 (4 9)
Quıte a bıt	38 (14 3)
Moderately	43 (16 2)
Slıghtly	81 (30 6)
Not at all	33 (12 5)
Have had no SOB	57 (21 5)
Symptom stabılıty	
Much worse ın past month	5 (1 9)
Slıghtly worse	25 (9 4)
Unchanged ın past month	120 (45 3)
Slıghtly better ın past month	36 (13 6)
Much better ın past month	38 (14 3)
No symptoms ın past month	41 (15 5)

Total depressive symptom scores ranged from 0 to 18 with no or minimal depressive symptoms reported by most (55 1%) participants As shown in Table 2, the mean PHQ-9 score was below the threshold for even mild depression Table 5 provides frequencies for each of the psychological symptoms measured Ninety (34 0%) participants had a total depression score indicative of mild depression, 26 (9 8%) had a score indicative of moderate depression, and 3 (1 1%) had a score indicative of moderately severe depression Most (64 2%) subjects reported no difficulty with working, taking care of things at home, or getting along with people because of depressive symptoms

Descriptive statistics for physical and social functioning are provided in Table 2 Frequencies for specific responses to each physical and social activity measured are provided in Table 6 Physical functioning scores ranged from 0 to 100 Thirty-one (11 7%) subjects received a score of 100, indicating no physical limitations due to HF during participation in 3 or more of the listed activities Most participants were physically limited by fatigue or SOB if they climbed a flight of stairs without stopping or participated in yardwork, housework, or carrying groceries within the previous month Of those who reported hurrying or jogging, as if to catch a bus, within the past month, most (62 0%) reported being quite a bit or extremely limited by HF during the activity Social functioning scores also ranged from 0 to 100, though the mean score was slightly lower than that for physical functioning More than half of the participants reported that fatigue or SOB limited participation in activities related to hobbies, chores, or intimate relationships Only 46 (17 4%) participants indicated no social limitations due to HF during participation in at least 2 of the listed activities

Table 5

Psychological Symptoms of Depression (N=265)

Variable	N (%)
Total score of 10 or more (major depression)	29 (10 9)
Somatic Symptoms	
Fatigue	194 (73 2)
Appetite problems	88 (33 2)
Sleeping difficulty	137 (51 7)
Psychomotor retardation or agitation	45 (17 0)
Cognitive Symptoms	
Lack of interest	84 (31 7)
Depressed mood	102 (38 5)
Worthlessness	57 (21 5)
Concentration problems	67 (25 3)
Suicidal ideation	7 (2 6)
Difficulty functioning due to depressive symptoms	95 (35 8)

Table 6

Physical and Social Functioning Responses (N=265)

Variable	N (%)
Physical Activities Limited by SOB or Fatigue	
Dressing (n=262)	54 (20 6)
Bathing or showering (n=260)	48 (18 5)
Walking one block on level ground (n=259)	125 (48 3)
Doing yardwork, housework, or carrying groceries (n=258)	197 (76 4)
Climbing a flight of stairs without stopping (n=261)	171 (65 5)
Hurrying or jogging (n=234)	209 (89 3)
Social Activities Limited by HF	
Hobbies (n=249)	180 (72 3)
Working or Chores (n=261)	200 (76 6)
Family visits (n=259)	122 (47 1)
Intimate relationships (n=233)	133 (57 1)

Note SOB = shortness of breath, HF = heart failure Percentage calculated of those who had participated in the activity

Bivariate Relationships

Correlational relationships between the predictor variables and OPH are shown in Table 7 A strong association was evident between physical functioning and OPH while most of the proposed predictors were moderately associated with OPH including household income, fatigue, SOB, depressive symptoms, and social functioning Education level, comorbid burden measured by the CCI, number of chronic illnesses, diabetes, and symptom stability were each weakly correlated with OPH Age, gender, and atrial fibrillation (AF) were not correlated with OPH

Relationships between categorical predictors and OPH were assessed by statistical testing of differences between groups with independent *t*-tests or ANOVA OPH was higher in females (M = 44 16, SD = 25 41) as compared to males (M = 38 73, SD = 27 24), but the difference was not significant (t(263) = -1 59, 95% CI [-12 14, 1 28], p = 11) OPH was higher in White subjects (M = 47 47, SD = 26 12) as compared to Asian (M = 33 00, SD = 15 87) or Black (M = 29 32, SD = 24 51) subjects (F(2,262) = 15 58, p < 001) Post hoc testing using Bonferroni correction revealed that the significant difference was between the White and Black groups (p < 001) OPH was also significantly higher in participants with a Bachelor's degree or graduate level education (M = 53 68, SD = 26 41) as compared to those with less education (M = 35 92, SD = 25 21) (t(263) = -5 01, 95% CI [-24 73, -10 78], p < 001) OPH also differed between those who reported a family income described as more than enough to make ends meet (M = 54 83, SD = 24 02), those who reported enough to make ends meet (M = 34 95, SD = 24 78), and those with not enough to make ends meet (M = 26 95, SD = 24 36) (F = 26 16, df 2, 262, p< 001) Post hoc testing using Bonferroni correction revealed that the

Table 7
Intercorrelations between Outcome and Predictor Variables (N=265)

	Age	Gender	Education	Income	# CI	CCI	Diabetes	Atrial Fib	Fatigue	SOB	Symptom Stability
OPH	07	10	25***	39***	- 27***	- 27***	- 20**	- 06	38***	45***	18**
Age	-	- 12*	- 11	18**	34***	25***	12*	11	22***	08	08
Gender		-	- 01	- 06	- 22***	- 22***	- 11	- 15*	- 15*	02	- 00
Education			-	28***	- 16**	- 10	- 15*	00	04	18**	- 00
Income				-	- 08	- 02	- 09	03	28***	33***	- 04
# CI					-	71***	48***	40***	- 00	- 16**	03
CCI						-	46***	08	- 05	- 16*	04
Diabetes							-	11	00	- 07	02
Atrial Fib								-	14*	- 03	- 09
Fatigue									-	60***	15*
SOB										-	22***
Symptom Stability											-

Note Values for race/ethnicity, education, and income are reported as Spearman's rho, all other values reported as Pearson's r correlation coefficient OPH = overall perceived health, # CI = number chronic illnesses, CCI = Charlson Comorbidity Index, Fib = fibrillation, SOB = shortness of breath

*p < 05 **p < 01 ***p < 01

Table 7 (continued)

Intercorrelations between Outcome and Predictor Variables (N=265)

	Depressive Symptoms	Physical Functioning	Social Functioning
OPH	- 32***	51***	49***
Age	- 18**	- 01	12
Gender	14*	- 02	11
Education	- 12*	21**	13*
Income	- 17**	38***	37***
# CI	01	- 28***	- 16**
CCI	04	- 22***	- 16*
Diabetes	03	- 11	- 11
Atrial Fib	- 02	- 01	- 03
Fatigue	- 54***	54***	68***
SOB	- 40***	68***	65***
Symptom Stability	- 14*	16**	14*
Depressive Symptoms	-	- 38***	- 42***
Physical Functioning		-	71***
Social Functioning			-

Note Values for education, and income are reported as Spearman's rho, all other values reported as Pearson's r correlation coefficient OPH = overall perceived health, # CI = number chronic illnesses, CCI = Charlson Comorbidity Index, Fib = fibrillation, SOB = shortness of breath

$^{*}p <$ 05 $^{**}p <$ 01 $^{***}p <$ 01 significant difference was between those with more than enough to make ends meet and each of the other two groups (p< 001) OPH was significantly lower in subjects with a history of diabetes (*M* = 33 90, *SD* = 22 90) as compared to those with no history of diabetes (*M* = 44 98, *SD* = 28 05) (*t*(247) = 3 51, 95% CI [4 87, 17 29], *p* = 001) There was no difference in OPH between those with AF (*M* = 38 53, *SD* = 26 84) and those without AF (*M* = 41 70, *SD* = 26 61) (*t*(263) = 91, CI [-3 73, 10 06], *p* = 37)

As evident in Table 7, several proposed predictors were significantly correlated with each other Both physical functioning and social functioning were strongly correlated with each other as well as with fatigue and SOB and were moderately correlated with depressive symptoms and income Fatigue was also strongly correlated with SOB and depressive symptoms, and SOB was moderately correlated with depressive symptoms and income Number of chronic illnesses and comorbid burden were strongly correlated with each other and moderately correlated with diabetes Number of chronic illness was also moderately correlated with atrial fibrillation and age Numerous weak correlations between multiple predictor variables were also statistically significant Relationships between descriptive variables and OPH were also tested using the statistical tests appropriate for the level of data OPH was significantly higher in married (*M* = 45 49, *SD* = 27 08) as compared to unmarried (*M* = 34 95, *SD* = 25 11) subjects (*t*(260) = -3 28, 95% CI [-16 86, -4 21], *p* = 001) OPH also differed significantly between NYHA groups (*F*(3, 261) = 18 412, *p* < 001) Post hoc testing with Bonferroni correction revealed that OPH was significantly lower in those classified as NYHA III (*M* = 40 56, *SD* = 24 47) as compared to those classified as NYHA I (*M* = 71 58, *SD* = 22 51) (*p* < 001) or II (*M* = 52 27, *SD* = 26 22) (*p* = 03) and in those classified as NYHA

IV (M = 23 18, SD = 22 68) as compared to each of the other levels ($p <$ 001 for all) EF was not correlated with OPH (r = - 03, p = 66) and OPH did not differ significantly by type of HF (F(2, 262) = 2 30, p = 11)

Regression

Aim #1 The first aim of this study was to determine the extent to which OPH levels in persons with HF are predicted by the individual characteristics of age, gender, race/ethnicity, education, and income To achieve this aim all variables were entered simultaneously into the first block of a hierarchical regression analysis The variables accounted for 22 4% of the variance in OPH, dropping to 20 5% after adjustment for the number of the variables, F(6,258) = 12 38, $p <$ 001 Coefficients for each variable are provided in Table 8

Several variables were significant predictors of OPH in this model Income was the strongest predictor with a higher income predicting better OPH Gender was also significant with female gender associated with a better OPH Being Black compared to White significantly predicted worse OPH Age, education, and Other race/ethnicity were not significant predictors of OPH in this model However, all variables were retained in the model because of theoretical importance Age was also retained to preserve hierarchy as several interactions involving age were planned for subsequent analyses

Aim #2 The second aim of this study was to determine the extent to which OPH levels in persons with HF, controlling for age, gender, race/ethnicity, education, and income, are uniquely predicted by each of several patient health variables

Aim #2a biophysiological variables (number of chronic illnesses, comorbid burden, diabetes, atrial fibrillation)

Aim #2b physical symptoms (fatigue, shortness of breath, symptom stability) beyond what is explained by the biophysiological variables

Aim #2c psychological symptoms (depression) beyond what is explained by biophysiological and physical symptom variables

Aim #2d functional status (physical functioning, social functioning) beyond what is explained by biophysiological, physical symptom, and psychological symptom (depression) variables

To achieve this aim a hierarchical regression analysis was performed with each set of variables listed in Aims #2a through 2d entered as blocks 2 through 5 in the sequence listed and depicted in the study model All variables in each block and the interaction of age with each variable other than the physical symptom variables were entered simultaneously During model building, substantial multicollinearity was noted between the interaction terms and their associated individual variables Therefore, continuous variables were centered to the mean and the interaction terms were recomputed using the centered variables Following this step, the collinearity statistics were significantly improved with variance inflation factors less than 5 for all variables No violations of the assumptions of linear ordinary least-squares regression were found and no transformations of the data were necessary

An evaluation of the contribution of each variable was also conducted during model building. Atrial fibrillation was not retained in the final model because it offered no significant information and its relationship to OPH was theoretically weak and supported by only one prior study. Diabetes was also not retained in the model because it offered no significant information when either of the more inclusive measures of comorbidity was also included. Number of chronic illnesses was not retained because it offered no significant information when comorbid burden measured by the CCI was included in the model. In contrast, the CCI score was a significant predictor of OPH even when number of chronic illnesses was included in the model. Only one of the age interaction terms, age by comorbid burden, was retained in the final model because the others offered no significant information to the model and were supported by only one prior study. When physical and social functioning were added in the last step of the regression analysis, neither of the coefficients were significant ($t = 1.72$, $p = .09$ and $t = 1.40$, $p = .16$ respectively). When the model was tested with social functioning removed, the coefficient for physical functioning was significant ($t = 2.44$, $p = .02$) and two other variables, gender and Black race/ethnicity became significant predictors in the step. Both variables had been significant predictors in the model until social and physical functioning had been added. Because of the substantial theoretical and empirical support for both gender and race/ethnicity as predictors of OPH and theoretical support and one prior study offering empirical support for gender influencing the effect of social functioning on OPH in a sample of Black subjects (CDC, 1996), interaction terms of gender by social functioning and Black race/ethnicity by social functioning were added to the model. The later term was not retained because it offered no significant information

However with the addition of the gender by social functioning interaction term to the model with physical functioning, social functioning and the interaction term were both significant predictors of OPH in the final model In this final step, the coefficient for physical functioning was not significant ($t = 1\ 68$, $p = \ 09$), but the variable was retained because of theoretical importance to the model and because the variance in OPH explained by the model was improved when it was included

The final model summary and the analysis of variance results for the final hierarchical regression analysis are provided in Table 8 The coefficients for each variable at each step in the model are provided in detail in Table 9

Aim #2a When controlling for age, gender, race/ethnicity, education, and income, the biophysiological variables of comorbid burden and the interaction of comorbid burden by age uniquely accounted for 6% of the variance in OPH As depicted in Table 8, the change in variance explained by the addition of these variables (Model 2) was significant, and the variance explained by the model was significant Comorbid burden was a significant independent predictor of OPH in this model with the effect significantly influenced by age (see Table 9, Step 2) As comorbid burden increases, OPH decreases with the negative influence stronger among younger patients Number of chronic illnesses, diabetes, and atrial fibrillation did not contribute to the variance in OPH

Aim #2b When controlling for age, gender, race/ethnicity, education, and income, the physical symptoms of fatigue, SOB, and symptom stability explained an additional 10 5% of the variance in OPH beyond what was explained by the biophysiological variables As depicted in Table 8, the change in variance explained by the addition of

Table 8

Model Summary for Hierarchical Regression on Overall Perceived Health (N=265)

Model	*# of Predictors*	R^2	Adjusted R^2	*SE* of the Estimate	R^2 Change	*p*
1	6	224	205	23 78	224	< 001
2	8	282	260	22 95	059	< 001
3	11	388	361	21 33	105	< 001
4	12	398	369	21 18	010	038
5	15	426	392	20 81	028	008

Note # = number For all models, the *p* value for the test of R^2 was < 001

Table 9

Coefficients from the Hierarchical Regression Analysis for Predictors of Overall Perceived Health (N=265)

Variable	*B*	*SE B*	β	*t*	*p*
Step 1					
Constant	10 281	6 501		1 58	12
Age	057	123	026	46	64
Gender	7 081	3 073	128	2 30	**.02**
Black versus white	-11 016	3 381	- 197	-3 26	**< .01**
Other versus white	-10 446	8 173	- 071	-1 28	20
Education	2 420	1 396	104	1 73	08
Income	11 519	2 314	301	4 98	**< .001**
Step 2					
Constant	8 345	6 356		1 31	19
Age	213	123	099	1 72	09
Gender	5 071	3 038	091	1 67	10
Black versus white	-8 302	3 320	- 148	-2 50	**.01**
Other versus white	-9 085	7 909	- 062	-1 15	25
Education	2 450	1 349	105	1 82	07
Income	11 851	2 240	310	5 23	**< .001**
Comorbid burden	-4 160	943	- 258	-4 41	**< .001**
Age by comorbid burden	166	074	123	2 23	**.03**

Step 3					
Constant	-14 003	7 105		-1 97	05
Age	095	117	044	81	42
Gender	5 825	2 866	105	2 03	**.04**
Black versus white	-6 919	3121	- 124	-2 22	**.03**
Other versus white	-5 028	7 394	- 034	- 68	50
Education	2 174	1 267	093	1 72	09
Income	9 089	2 179	238	4 17	**< .001**
Comorbid burden	-3 473	890	- 216	-3 90	**< .001**
Age by comorbid burden	140	070	104	2 01	**.05**
Fatigue[a]	136	059	150	2 30	**.02**
SOB[a]	153	059	170	2 57	**.01**
Symptom stability[a]	169	061	142	2 76	**.01**
Step 4					
Constant	-9 267	7 413		-1 25	21
Age	073	117	034	62	53
Gender	6 365	2 859	115	2 23	**.03**
Black versus white	-7 215	3 103	- 129	-2 32	**.02**
Other versus white	-5 476	7 348	- 037	- 74	46
Education	1 839	1 269	079	1 45	15
Income	9 285	2 166	243	4 29	**< .001**
Comorbid burden	-3 435	884	- 213	-3 89	**< .001**

Age by comorbid burden	151	069	112	2 18	**.03**
Fatigue[a]	083	064	092	1 31	19
SOB[a]	142	059	157	2 39	**.02**
Symptom stability[a]	163	061	137	2 68	**.01**
Depressive symptoms	-9 10	435	- 125	-2 09	**.04**
Step 5					
Constant	76 319	8 902		0 71	48
Age	115	116	054	1 00	32
Gender	5 703	2 950	103	1 93	05[b]
Black versus white	-6 386	3 088	- 114	-2 07	**.04**
Other versus white	-4 483	7 243	- 030	-0 62	54
Education	1 671	1 249	072	1 34	18
Income	7 868	2 189	206	3 59	**< .001**
Comorbid burden	-2 990	883	- 186	-3 38	**< .01**
Age by comorbid burden	100	070	074	1 43	15
Fatigue[a]	015	070	016	0 21	84
SOB[a]	045	067	050	0 68	50
Symptom stability[a]	150	060	125	2 49	**.01**
Depressive symptoms	- 832	431	- 114	-1 93	05[b]
Physical functioning[a]	152	091	135	1 68	10
Social functioning[a]	185	087	195	2 12	**.04**
Gender by social functioning	- 202	099	- 123	-2 04	**.04**

Note Gender coding was 0 for males and 1 for females Race/ethnicity coding was 0 for white and 1 for black or for other SOB = shortness of breath [a]higher score indicates better health, [b]actual $p =$ 054 $R^2 =$ 20 for Step 1 ($p <$ 001), $\Delta R^2 =$ 06 for Step 2 ($p <$ 001), $\Delta R^2 =$ 10 for Step 3 ($p <$ 001), $\Delta R^2 =$ 01 for Step 4 ($p =$ 04), $\Delta R^2 =$ 03 for Step 5 ($p <$ 01) these variables (Model 3) was significant, and the variance explained by the model was significant When controlling for all other variables in the model, each of the physical symptom variables was a significant independent predictor of OPH in the model (See Table 9, Step 3) As symptom health improves (i e , the burden of frequency and bothersomeness lessens) for either fatigue or SOB, OPH increases Also, as symptom worsening lessens or symptoms improve over the previous month, OPH increases

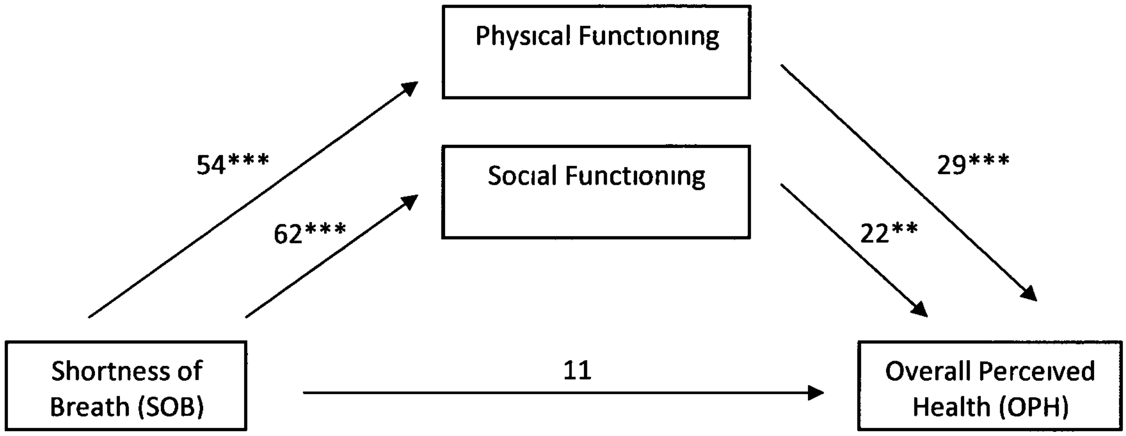
Aim #2c When controlling for age, gender, race/ethnicity, education, and income, psychological symptoms of depression explained an additional 1% of the variance in OPH beyond what was explained by the biophysiological and physical symptom variables As depicted in Table 8, the change in variance explained by the addition of this variable (Model 4) was significant and the variance explained by the model was significant When controlling for all other variables in the model, the depressive symptom variable was a significant independent predictor of OPH (See Table 9, Step 4) As depressive symptoms increase, OPH decreases

Aim #2d When controlling for age, gender, race/ethnicity, education, and income, the functional status variables of physical functioning and social functioning, with the addition of a gender by social functioning interaction term, explained an additional 3% of the variance in OPH beyond what was explained by the biophysiological, physical symptom and psychological symptom variables As depicted in Table 8, the change in variance explained by the addition of these variables (Model 5) was significant, and the variance explained by the model was significant When controlling for all other variables in the model, social functioning and gender by social functioning interaction were significant independent predictors of OPH (See Table 9, Step 5) The relationship of social functioning and OPH is significantly different in males and females In males, as social functional status improves, OPH increases ($B =$ 185) In females, this coefficient is - 017, found to be non-significant (p = 87) when gender was reverse coded

Final Regression Model Interpretation The final model containing 15 variables explained 39 2% of the variance in OPH after adjustment for the number of variables The 6 variables in the model that were significant independent predictors of OPH, listed in descending order by the size of their standardized coefficients, include income, social functioning, comorbid burden, physical symptom stability, gender by social functioning, and Black race/ethnicity Higher OPH was predicted by higher income, symptom stabilization or improvement, and, in males only, higher social functioning Lower OPH was predicted by higher comorbid burden and Black as compared to White race/ethnicity The other 9 variables collectively contributed to the explanation of the variance in OPH, significantly increasing the R^2 value, but none offered significant *unique* contributions These included higher age, female gender, more education, lower fatigue burden, lower SOB burden, and higher physical functioning predicting higher OPH, depressive symptoms and Other as compared to White race/ethnicity predicting lower OPH, and the age by comorbid interaction term indicating that the negative association between comorbid burden and OPH was stronger among younger patients Gender and depressive symptoms were actually borderline in their significance the p value for each coefficient was 054 It is important to note key changes in coefficient values and significance in several variables at each step in the hierarchical regression indicating a shared variance with added variables For example, when the variable for depressive symptoms was added to the model in step 4, the physical symptom of fatigue became a nonsignificant independent predictor with the unstandardized coefficient dropping from 0 136 to 0 083 The measure of depressive symptoms contained an item measuring fatigue as well as items measuring other somatic symptoms common in both HF and depression With the addition of physical and social functioning to the model in step 5, SOB and depressive symptoms became nonsignificant independent predictors of OPH The unstandardized coefficient value for depressive symptoms diminished slightly from -0 910 to -0 832, while the value change for SOB was pronounced, falling from 0 142 to 0 045 At this step also, the unstandardized coefficient for fatigue was again greatly reduced dropping from 0 083 to 0 015

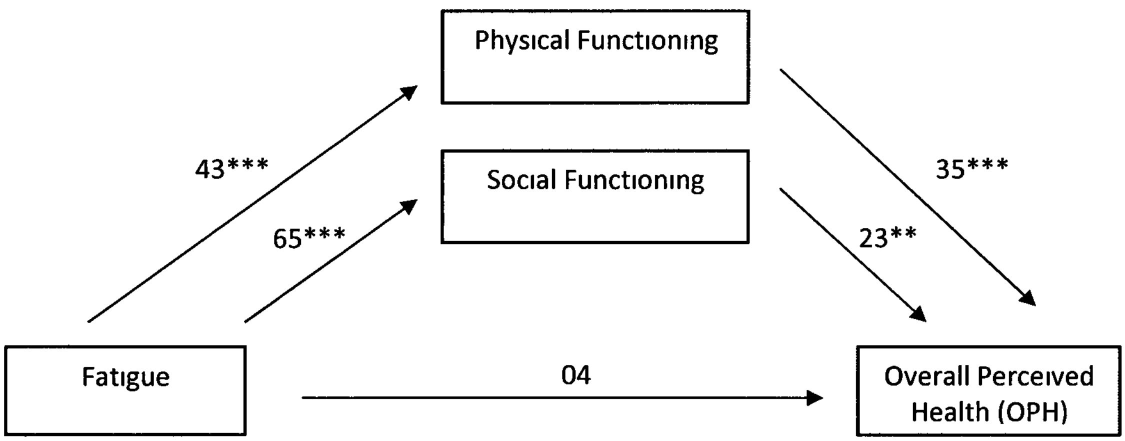
Mediation Analysis

The third aim of this study was to test whether functional status mediates the relationship between physical symptoms and OPH To achieve this aim, a multiple mediator analysis was conducted to assess the indirect effects of physical symptoms on OPH via physical functioning and social functioning using bootstrapping with nonparametric resampling with replacement 1,000 times to determine 95% confidence intervals of the effects As depicted in Figures 2 and 3, this aim was achieved with the finding that both physical and social functioning mediated the effect of SOB on OPH ($F(3, 261) = 37\ 42$, $p <\ 001$) and the effect of fatigue on OPH ($F(3, 261) = 36\ 33$, $p <\ 001$) Table 10 offers detailed information regarding each effect In both cases the total effect of symptoms on OPH was significant, but their direct effect (c’) on OPH was nonsignificant indicating total mediation of the effect of the physical symptom through the mediating variables The two indirect effects (ab) for each model were not



** < 01 *** < 001

Figure 2 Multiple mediation model of SOB on OPH through physical and social functioning with coefficients indicated for each path $R^2 = 30$, Adjusted $R^2 = 29$



** < 01 *** < 001

Figure 3 Multiple mediation model of fatigue on OPH through physical and social functioning with coefficients indicated for each path $R^2 = 29$, Adjusted $R^2 = 29$

significantly different from each other indicating that both physical functioning and social functioning equally mediate the influence of the symptom on OPH The contrast in indirect effects for SOB was 0 03, 95% CI [- 15, 20] and the contrast in indirect effects for fatigue was 0 002, 95% CI [- 16, 17] In both instances, the mediation model accounted for 29% of the variance in OPH

Because physical and social functioning were so highly correlated ($r =$ 71, $p <$ 001), individual mediation analyses were also performed in order to evaluate the effects of this collinearity on the model estimates Figures 4 and 5 offer graphic depictions of these models and Table 11 provides detailed information for each effect In all cases, the effects of the mediator on OPH (b) were higher than in the multiple mediator analysis producing an increase in the indirect effects (ab) In addition, the direct effects (c') of each of the symptoms on OPH with the exception of fatigue on social limitation were significant indicating only partial mediation of the symptom through the single functioning variable included in the analysis Physical functioning mediated the effects of SOB ($F(2, 262) =$ 50 15, $p <$ 001) and of fatigue ($F(2, 262) =$ 49 06, $p <$ 001) on OPH And social functioning mediated the effects of SOB ($F(2, 262) =$ 49 21, $p <$ 001) and fatigue ($F(2, 262) =$ 43 01, $p <$ 001) on OPH

In light of the discovery of a gender by social functioning interaction in the hierarchical regression analysis, a moderated mediation analysis was conducted to assess whether gender moderated the mediation of SOB or fatigue by social functioning Following the method recommended by Preacher, Rucker, and Hayes (2007), separate models were computed to test the conditional indirect effects of SOB and fatigue on OPH through social functioning in males and females Moderation of the mediation effects is

Table 10

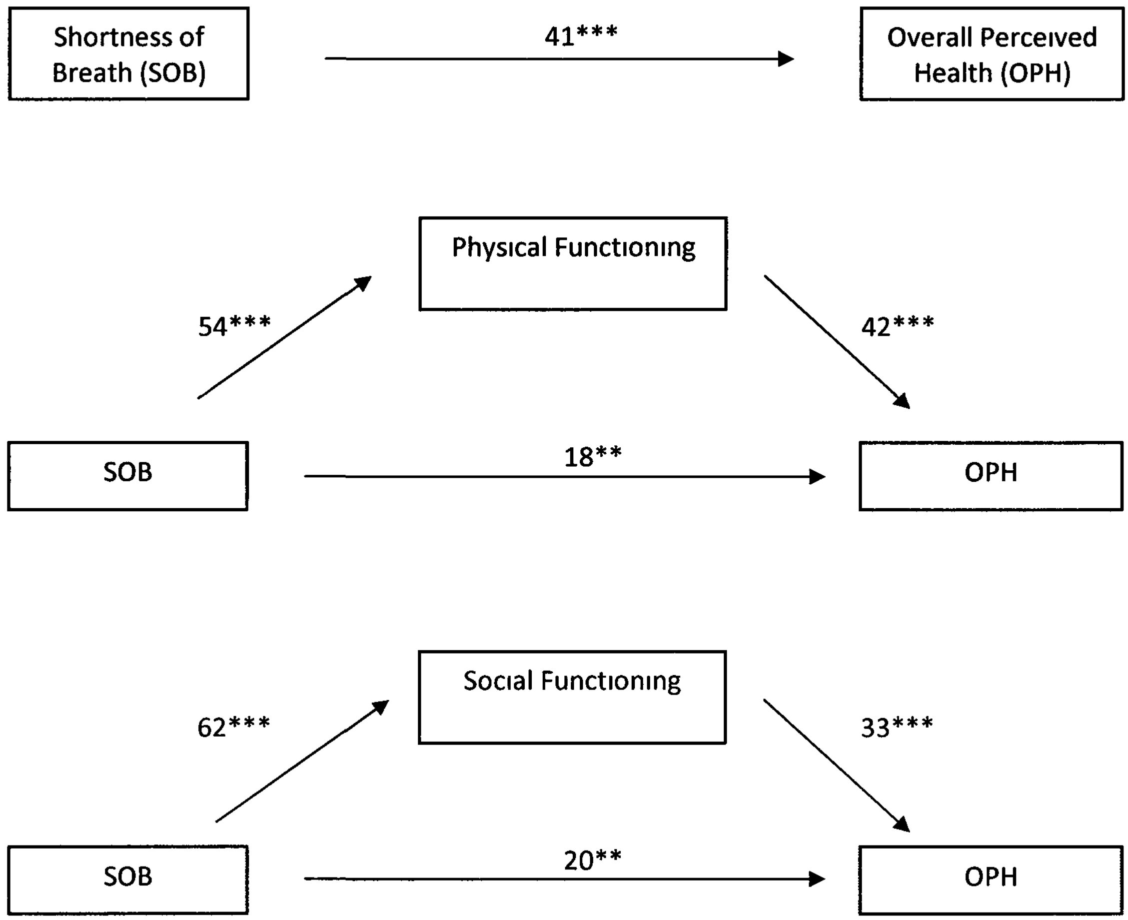
Summary of multiple mediator model analysis with 1000 bootstraps ($N = 265$)

IV	Mediating Variable (M)	Effect of IV on M (a)	Effect of M on DV (b)	Direct Effect (c')	Indirect Effect [a] (ab)	95% CI	Total Effect (c)
SOB				11			41***
	Physical FS	54***	29**		16	[05, 26]	
	Social FS	62***	22**		14[b]	[03, 23]	
Fatigue				04			34**
	Physical FS	43***	35***		15	[07, 23]	
	Social FS	65***	23**		15	[04, 25]	

Note IV = Independent Variable, DV = Dependent Variable, FS = functional status

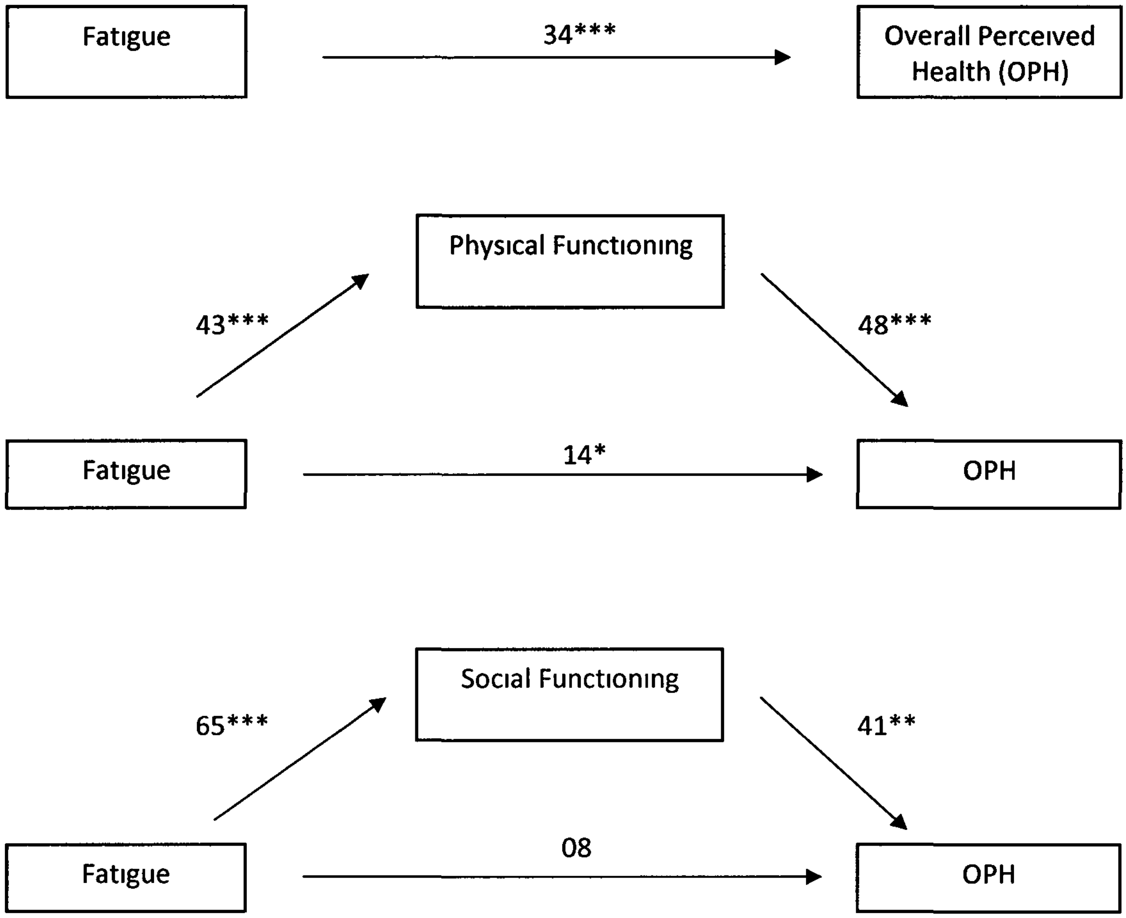
[a] Reported indirect effect values reflect both data and bootstrap estimates unless otherwise indicated, [b] value is bootstrap estimate - data estimate was 13

* < 05 ** < 01 *** < 001



*** < 001
** < 01

Figure 4 Individual mediation models of SOB on OPH, the first through physical functioning and the second through social functioning with coefficients indicated for each path For physical functioning model, R^2 = 27 and adjusted R^2 = 27 For social functioning model, R^2 = 27 and adjusted R^2 = 27



*** < 001
** < 01
* < 05

Figure 5 Individual mediation models of fatigue on OPH, the first through physical functioning and the second through social functioning with coefficients indicated for each path For physical functioning model, R^2 = 27 and adjusted R^2 = 27 For social functioning model, R^2 = 25 and adjusted R^2 = 24

Table 11

Summary of single mediator model analysis with 1000 bootstraps (*N* = 266)

IV	Mediating Variable (M)	Effect of IV on M (a)	Effect of M on DV (b)	Direct Effect (c')	Indirect Effect[a] (ab)	95% CI	Total Effect (c)
SOB	Physical FS	54***	42***	18**	23	[13, 33]	41***
	Social FS	62***	33***	20**	20	[11, 29]	
Fatigue	Physical FS	43***	48***	14*	21	[13, 28]	34***
	Social FS	65***	41***	08	27	[19, 36]	

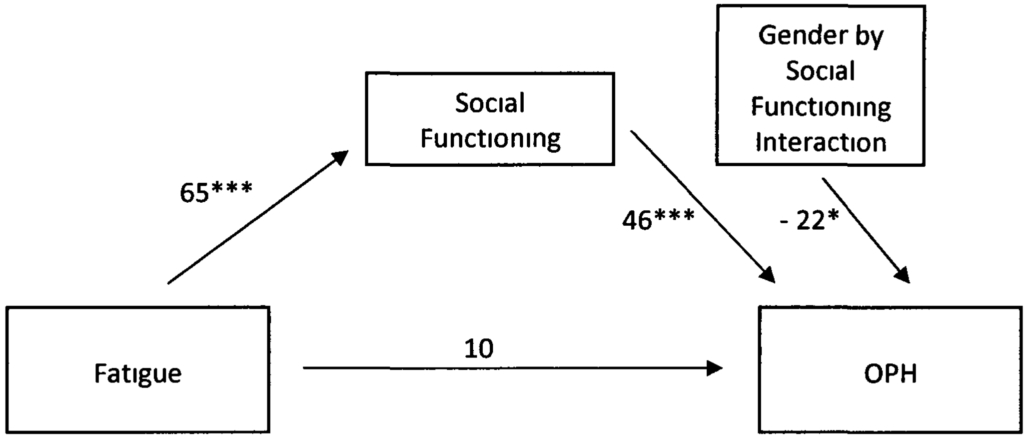
Note IV = Independent Variable, DV = Dependent Variable, FS = functional status

[a] Reported indirect effect values reflect both data and bootstrap estimates

* < 05 ** < 01 *** < 001

evident if the interaction term of the mediating and moderating variables is a significant predictor of the outcome variable in the model, i e , if the interaction effect of gender by social functioning on OPH is significantly different from zero, then a conditional effect is present Gender did *not* moderate the mediation of the influence of SOB on OPH by social functioning as evidenced by a nonsignificant interaction effect (B = -0 19, p = 07) However, as depicted in Figure 6, gender *did* moderate the mediation of the influence of fatigue on OPH by social functioning as evidenced by the interaction effect differing significantly from zero (B = -0 22, p = 04) The coefficient for the conditional indirect effect of fatigue on OPH mediated by social functioning for females was B = 15, p = 02, 95%CI [0 02, 0 28] and for males was B = 30, p < 001, 95% CI [0 20, 0 40] So, while physical and social functioning mediate the effect of fatigue on OPH, the mediation effect of social functioning is significantly stronger for males than it is for females

In summary, all three aims of this study were achieved In persons with HF the individual characteristics of age, gender, race/ethnicity, education, and income accounted for 20 5% of the variance in OPH Controlling for these variables, sets of biophysiological variables, physical symptoms, psychological symptoms, and functional status each uniquely accounted for a significant increase in variance in OPH In the final model a total of 15 variables accounted for 39 2% of the variance in OPH and 6 independent predictors were identified In addition, the effects of both fatigue and SOB on OPH were found to be fully mediated by both physical and social functioning with the mediation of fatigue on OPH by social functioning moderated by gender such that the effect was stronger in males as compared to females



* < 05 *** < 001

Figure 6 Moderated mediation models of fatigue on OPH through social functioning testing moderation by gender with coefficients indicated for each path The conditional indirect effect of fatigue on OPH is computed as 0 65[0 46 (social functioning) - 0 22 (gender)]

Chapter 5

Predictors of Overall Perceived Health in Patients with Heart Failure

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Abstract

BACKGROUND Overall perceived health (OPH) is a powerful and independent predictor of negative health outcomes and low health-related quality of life For reasons unknown, OPH is conspicuously low in patients with heart failure (HF) OBJECTIVE The purpose of this study was to determine the key variables associated with OPH in persons with HF and to evaluate the variability in OPH attributable to each METHODS This cross-sectional predictive correlational study was a secondary analysis of an existing dataset Individual characteristics, biophysiological variables, physical symptoms, psychological symptoms, and physical and social functioning were included as predictor variables in a five-step hierarchical regression analysis RESULTS The sample (n=265) was primarily male (64 2%), white (61 9%), with a mean age of 62 years, at least a high school education, and a household income enough or more than enough to meet needs Most (69 1%) had systolic dysfunction, and 78 5% were NYHA III or IV Individual characteristics explained 20 5% of the variance in OPH The final model containing 15 predictors explained 39 2% of the variance in OPH Six variables were significant independent predictors of OPH income, social functioning, comorbid burden, symptom stability, race/ethnicity, and the interaction of gender and social functioning, the later indicating social functioning was a stronger predictor for males than for females In a multiple mediation analysis, the effects of shortness of breath and fatigue on OPH were mediated by physical and social functioning Gender moderated the mediation of fatigue by social functioning CONCLUSIONS These variables explained a significant portion of the variance in OPH If OPH decreases or is low, a focus on patient symptoms and

ability to participate in life activities is appropriate, with particular attention to social functioning in men

Key Words perceived health, self-rated health, heart failure

Often described as the *cancer* of heart disease, HF is a progressive and complex clinical syndrome with no cure HF affects 5 7 million people in the United States (Roger et al , 2011) with an age-adjusted 5-year mortality estimate of 48% (Roger et al , 2004) For surviving HF patients, the need for rehospitalization is frequent (Hunt et al , 2009, Kosiborod, 2006) and HRQOL is poor (Calvert et al , 2005, Luttik et al , 2006, Hobbs et al , 2002) These negative health outcomes share one common independent predictor, low overall perceived health (OPH)

OPH is a subjective, individualized self-assessment of the current overall state of personal health that is typically measured by a single question asking for a rating of current general health status OPH is an independent and unique variable that is sensitive to psychological, physical, and social changes (Bailis, Segall, & Chipperfield, 2003, Benyamini, Leventhal, & Leventhal, 2003, Winter, Lawton, Langston, Ruckdeschel, & Sando, 2007) Importantly, OPH influences subsequent health behaviors (Balkrishnan, Anderson, & Christensen, 2002, DiMatteo, Haskard, & Williams, 2007, Zimmermann, Ekholm, Grønbæk & Curtis, 2008) Yet, no research has been conducted that focuses on OPH as a key to improving negative health outcomes in persons with HF Therefore, the purpose of this study was to examine the variables that significantly influence OPH in chronic HF patients Armed with an understanding of the factors that influence OPH, clinicians can potentially intervene in patients with decreasing or low OPH and possibly lessen their risk for negative outcomes or at least delay those that are inevitable

Background and Significance

OPH is significantly lower in HF patients than in the general population (Riedinger, Dracup, & Brecht, 2002), healthy age-peers (Heo, Moser, Lennie, Zambroski

& Chung, 2007), patients with other cardiovascular conditions such as coronary artery disease (CAD) and hypertension (Riedinger et al), and even patients with other chronic diseases such as depression, arthritis, and chronic obstructive pulmonary disease (COPD) (Riedinger et al) Commonly misconstrued as a proxy for HRQOL, OPH is a distinct construct that directly influences and significantly mediates the influence of other factors on HRQOL (Heo, Moser, Riegel, Hall, & Christman, 2005, Smith, Avis, & Assmann, 1999, Sousa & Kwok, 2006) OPH has been verified to be more than solely a personality trait (McCullough & Laurenceau, 2005, Moor, Zimprich, Schmitt, & Kliegel, 2006), enduring self-concept (Bailis, Segall, & Chipperfield, 2003), or simply a measure of declining health trajectory (Wolinsky & Tierney, 1998)

In patients with HF, OPH has been demonstrated to be a powerful predictor of worsening health (Havranek et al , 2001), need for hospitalization (Havranek et al , Konstam et al , 1996, Roe-Prior, 2004), mortality (Farkas, Nabb, Zaletel-Kragelj, Cleland, & Lainscak, 2009, Havranek et al , Johansson, Brostrom, Dahlstrom, & Alehagen, 2008, Konstam et al), and low HRQOL (Heo et al , 2005) even after controlling for demographic characteristics (Farkas et al , Havranek et al , Heo et al , Johansson et al, Konstam et al), comorbid conditions (Farkas et al , Heo et al , Johansson et al , Roe-Prior), New York Heart Association (NYHA) class (Heo et al , Johansson et al , Konstam et al), exercise tolerance (Havranek et al), clinical measures such as ejection fraction (EF) (Johansson et al , Konstam et al), estimated glomerular filtration rate (Farkas et al), hemoglobin (Farkas et al), or sodium B-type natriuretic peptide (Johansson et al), and treatment (Konstam et al)

Several factors have been identified as influencing OPH in studies using primarily population- or age-based sampling Age (Aalto et al , 2006, Benyamini, Leventhal & Leventhal, 2003, Brown, Ang, & Pebley, 2005, Gold, Franks, & Erickson, 1996, Hou & Myles, 2004, Menec, Shoostari, & Lambert, 2007, Shooshtari, Menec, & Tate, 2007, Wang, 2008), gender (Aalto et al , Bayliss, Ellis, & Steiner, 2007, Brown et al , Diehr, Williamson, Patrick, Bild, & Burke, 2001, Farmer & Ferraro, 1997, Gold et al , Hou & Myles, Menec et al , Shooshtari et al , Wang et al), race/ethnicity (Diehr et al 2001, Farmer & Ferraro, 1997, Gerber, Benyamini, Goldbourt, & Drory, 2009, Gold et al , Menec et al), education, (Bayliss et al , Brown et al , Farmer & Ferraro, Gerber et al , Gold et al , Hou & Myles, Jylha, Colpato, & Guralnik, 2006, Menec et al , Shooshtari et al , Wang), and income (Bayliss et al , Brown et al , CDC, 1996, Farmer & Ferraro, Gerber et al , Gold et al , Hou & Myles, Shooshtari et al , Wang) have demonstrated association with OPH, though some researchers have found conflicting results (Diehr, et al , Farmer & Ferraro, Winter et al , 2007) Others have demonstrated an interaction effect between one or more of these characteristics with each other or with other variables (Aalto et al , Schnittker, 2005, Xie, et al, 2008) Only two studies have focused on the relationship between these characteristics and OPH in patients with HF In a sample of 186 urban residents with low education and limited resources, higher age was the only significant demographic characteristic predictive of better OPH in a model explaining 14% of the variance that included gender, race, education, and income as well as EF, comorbidity, social-cognitive factors and social support (Clark et al) In a sample (n=146) that was 91% male and limited to patients with systolic ventricular dysfunction, only a non-sıgnıficant dırect effect of ıncome was found (Rosen, Contrada, Gorkın, & Kostıs, 1997)

An ınverse relatıonshıp between the number and/or severıty of chronıc ıllnesses and OPH ıs well documented ın multıple studıes (Baılıs et al , 2003, Baylıss et al , 2007, Brown et al , 2005, Gerber et al , 2009, Jylha et al , 2006, Menec et al , 2007, Shooshtarı et al , 2007) In addıtıon, several specıfic chronıc condıtıons have been found to be sıgnıficantly assocıated wıth lower OPH ıncludıng HF (Calvert et al , 2005, Geobel, Doerıng, & Evangelısta, 2009, Gold et al , 1996, Heo et al , 2007, Rıedınger et al , 2002), coronary heart dısease (Gold et al , Xıe et al , 2008), hypertensıon (CDC, 1996, Gold et al), COPD (Gold et al), stroke (Gold et al , Jylha et al), cancer (Gold et al , Jylha et al), dıabetes (CDC, Gerber et al, Gold et al , Jylha et al), and atrıal fibrıllatıon (Berry, Stewart, Payne, McArthur & McMurray, 2001) Only one study has examıned the ınfluence of other chronıc ıllness on OPH ın HF patıents and no assocıatıon was found, but these findıngs are lımıted by the use of bıllıng codes to measure comorbıd burden (Clark et al , 2003)

Physıcal symptoms have consıstently been shown to have a strong and adverse assocıatıon wıth OPH ın numerous studıes (Aalto et al, 2006, Benyamını et al , 2003, Nguyen, Donesky-Cueno, & Kohlman, 2008, Shooshtarı et al , 2007, Sousa & Kwok, 2006, Walke, Byers, Gallo, Endrass & Frıed, 2007, Wınter et al , 2007) Also, a *change* ın symptoms or symptom ıntensıty has been found to be predıctıve of OPH (Wınter et al) Specıfically, fatıgue, alone or ın combınatıon wıth SOB, has been found to have a negatıve relatıonshıp wıth OPH ın multıple populatıons (Benyamını et al , Nguyen et al , Smıth et al 1999, Sousa & Kwok, Walke et al), ıncludıng patıents wıth HF (Heo et al , 2005, Sullivan et al , 2007) However, sampling in the HF studies was limited to patients hospitalized with acute exacerbation of their condition (Heo et al) or to patients with severely advanced HF (Sullivan et al) The relationship between physical symptoms and OPH has been postulated to be mediated by functional status (Wilson & Cleary, 1995, Ferrans, Zerwic, Wilbur, & Larson, 2005), and this relationship has been tested in patients with HIV Using structural equation modeling, Sousa and Kwok found both a direct relationship between symptoms and OPH and as well as a mediation effect through functional status In contrast, in a sample of hospitalized HF patients others found no mediation effect (Heo et al) These relationships have not been studied in the general population of HF patients

A negative relationship between depressive symptoms and OPH is also well documented in the general population (Brown et al , 2005, Bryant et al , 2000, Han, 2002, Schnittker, 2005), older adults with chronic illness (Bayliss et al , 2007) or functional disability (Han & Jylha, 2006), and in persons who have experienced a myocardial infarction (Gerber et al , 2009) However, in a longitudinal analysis using an autoregressive, cross-lagged panel design in a large population sample, investigators found little influence of depressive symptoms on OPH, but a significant and consistent influence of OPH on depressive symptoms (Kosloski, Stull, Kercher, & Van Dussen, 2005) In patients with HF, a negative relationship was found between depression and OPH in a sample of patients with markedly advanced disease (Sullivan et al 2007) In another sample limited to patients with systolic dysfunction and 91% male, an index of emotional distress that included depressive symptoms and 3 other psychological domains was a significant predictor of lower OPH (Rosen et al , 1997)

Physical functioning has consistently been demonstrated to be the strongest predictor of OPH identified to date (Bailis et al , 2003, Bayliss et al , 2007, Benyamini et al , 2003, Katz et al , 2008, Menec et al , 2007, Shooshtari et al , 2007, Sousa & Kwok, 2006), and this relationship was found in the HF study limited to patients with systolic dysfunction (Rosen et al , 1997) In contrast, no significant relationship between physical functional status and OPH was found in hospitalized HF patients (Heo et al , 2005) Social functioning has been demonstrated to be a predictor of OPH in a large population based study (Bailis et al), two studies of patients with chronic illness (Bayliss et al , Katz et al), and the sole meta-analysis of health domains related to OPH (Smith et al , 1999)

In spite of the low values of OPH and its predictive validity for poor health outcomes in persons with chronic HF, few studies have focused on this construct in this population and the findings from these have limited generalizability due to restricted sampling or available data No study of the key factors known to predict OPH in other populations has been conducted in a typical community-dwelling, general sample of patients living with HF This study was designed to determine the key variables associated with OPH in persons with chronic HF and to evaluate the amount of variability in OPH attributable to each using a hierarchical regression analysis Further analysis of the relationship between symptoms and functional status was also indicated by the conflicting findings in the literature as to whether symptoms directly relate to OPH or are mediated by functional status Therefore, the specific aims of this study were twofold First we sought to assess the extent to which OPH levels in persons with HF are uniquely predicted by each of several sets of patient variables individual characteristics (i e , age, gender, race/ethnicity, education, income), biophysiological variables (number of chronic illnesses, comorbid burden, diabetes, atrial fibrillation), physical symptoms (fatigue, shortness of breath, symptom stability), psychological symptoms (depression), and functional status (physical functioning, social functioning) Second, we wanted to test whether functional status mediates the relationship between physical symptoms and OPH

Conceptual Framework

The conceptual framework for this study was based on the Wilson and Cleary (1995) Model (WCM) of patient outcomes, a conceptual model of HRQOL, as refined by Ferrans et al (2005), with substantiation from a conceptual model of OPH postulated by Jylha (2009) The WCM consists of a causal pathway with five levels of increasing integration and complexity biophysiological factors, symptoms, functioning, general health perceptions, and overall quality of life, with individual and environmental characteristics postulated to influence each General health perceptions are conceptualized as reflecting integration of the components depicted earlier in the model The concept of general health perceptions is widely invoked in health outcomes research and encompasses personal self-evaluations of health in general without focus on specific health dimensions (i e , physical health, mental health, functioning) (Davis & Ware, 1981, PROMIS, 2008) Although general health perceptions include several domains such as prior health, health outlook, and resistance to illness, OPH, as current health, has been clearly identified as the core domain (Davis & Ware) Therefore, the major portion of the WCM offers a framework of factors thought to influence OPH

Focusing on OPH as an individual and subjective conception, Jylha's conceptual model depicts the *process* of individual health evaluation by delineating three stages in this self-assessment and identifying the factors considered in each of those stages The initial stage involves a personal review of the key concepts included in the WCM lumped together in no particular order without consideration of a sequential influence of one on another The second stage includes a personal consideration of age

The WCM was modified to create the study model, depicted in Figure 1, based on empiric delineation of specific variables that influence OPH and model testing by other researchers (Heo et al , 2005, Sousa and Kwok, 2006) In the study model, direct relationships between each variable and OPH are depicted rather than the sequential linear relationships culminating in OPH depicted in the WCM This manner of depiction was used because direct relationships are theoretically feasible and substantiated by numerous studies

Methods

Design and Samples

A cross-sectional descriptive and predictive design was used to conduct a secondary analysis of baseline data from patients with HF recruited between 2007 and 2009 for a prospective study examining the influence of excessive daytime sleepiness (EDS) on self-care, HRQOL, and unplanned hospitalization (conducted by BR) For the parent study, subjects were identified from outpatient settings in Philadelphia, PA and Newark, DE Inclusion criteria included Stage C chronic HF confirmed by echocardiography and clinical evaluation, ability to speak and read English, adequate literacy, hearing adequate to engage in dialogue, and living in a setting amenable to performing self-care Patients were excluded if they had major depression, severe dementia or significant cognitive impairment at the time of screening, renal failure requirıng dıalysıs, nıght shıft work, termınal ıllness, planned relocatıon, or heavy and regular drug or alcohol abuse wıthın the past year More detaıled ınformatıon about the samplıng and recruıtment of subjects ın the parent study has been publıshed elsewhere (Rıegel, et al , ın press) For thıs secondary analysıs all data were obtaıned wıthout ıdentıfyıng ınformatıon and the study was approved by the Unıversıty of Nebraska Medıcal Center ınstıtutıonal revıew board

A power analysıs was performed usıng GPower 3 010 A sample sıze of 120 was requıred for a hıerarchıcal regressıon analysıs wıth a specıal R^2 ıncrease of 5% for the final step wıth a power of 80 and ındıvıdual regressıon coefficıent alpha = 05 For the medıatıon analysıs, guıdelınes offered by Frıtz and MacKınnon (2007) suggested that at least 162 subjects were needed Estımates were exceeded by the avaılable sample

In all, 280 subjects were enrolled ın the parent study Fourteen dıd not have the data needed for thıs study These patıents dıffered from the remaınıng sample ın that they had sıgnıficantly better health ın terms of NYHA class, physıcal and psychologıcal symptoms, and physıcal functıonıng The data for one addıtıonal subject was not used ın thıs analysıs because of contradıctory and ıncompatıble responses on a key measure Therefore, the final sample for thıs study consısted of 265 patıents wıth symptomatıc HF

Measures

OPH was measured wıth the commonly used first ıtem ın the SF-36 (v2) often referred to as self-rated health The self-rated health ıtem states "In general, would you say your health ıs " wıth response choıces of *excellent, very good, good, faır, or poor* The Medıcal Outcomes Study scorıng algorıthm was used to recalıbrate the response scale and to convert scores to a 0-100 scale wıth 0 ındıcatıng "poor" and 100 ındıcatıng “excellent” (Ware, Kosınskı, & Dewey, 2000) The self-rated health ıtem has been used extensıvely ın healthcare research for over 30 years as a subjectıve assessment of overall health both ın the general populatıon and ın subjects wıth a wıde varıety of medıcal condıtıons ıncludıng HF (Benyamını et al , 2003, Davıes & Ware, 1981, Dıehr et al, 2001, Heo et al , 2007, Heo et al , 2005, Rosen et al , 1997) Construct and dıscrımınant valıdıty of thıs measure have been well establıshed (Cunny & Perrı, 1991, DeSalvo et al , 2006, McHorney, Ware, Lu, & Sherbourne, 1994) Responsıveness of the SRH ıtem was supported ın two longıtudınal studıes demonstratıng changes ın SRH ın response to changes ın predıctor varıables ın the general populatıon (Baılıs et al , 2003, Farmer & Ferraro, 1997)

Age, gender, race/ethnıcıty, educatıon, and famıly ıncome were measured wıth a socıodemographıc questıonnaıre desıgned specıfically for the parent study Type, severıty and duratıon of HF were collected from the medıcal record and used only to descrıbe the sample Chronıc ıllness was measured wıth four dıstınct varıables ıdentıfied ın the lıterature as related to OPH (a) number of chronıc ıllnesses, (b) comorbıdıty burden operatıonalızed as an ındex of number and severıty of chronıc ıllnesses, (c) dıagnosıs of dıabetes, and (d) dıagnosıs of chronıc atrıal fibrıllatıon Chronıc ıllness data were collected from medıcal record revıew The Charlson Comorbıdıty Index (CCI) total score was used to measure comorbıd burden Construct valıdıty of the CCI has been confirmed ın the HF populatıon[65] and the medıcal record format used ın thıs study has been used frequently ın HF patıents (Chın & Goldman, 1997) and the medıcal record format used ın thıs study has been used frequently ın HF patıents (Blınderman et al , 2008, Heo et al , 2005, Rıegel, Carlson, Glaser, & Romero, 2006)

Physical symptoms and physical and social functioning were measured with the Kansas City Cardiomyopathy Questionnaire (KCCQ), a HF-specific health status measure (Green, Porter, Bresnahan, & Spertus, 2000) Items on the KCCQ refer to the respondent's health during the previous 2 weeks, but the time frame was changed to 1 month for the parent study Using the guidelines described by the KCCQ authors, subscale scores were computed and transformed to a 0 to 100 range with higher values indicating better health status Content and construct validity of the KCCQ as well as adequate internal consistency and test-retest reliabilities for each of the subscales have been established (Green et al) Internal consistency reliability of the physical and social functioning subscales in this study sample was adequate with Cronbach's alpha values of 85 and 86 respectively Instead of the KCCQ physical symptom subscale score, individual scores for fatigue and shortness of breath (SOB) using the same computation strategy were computed from each identical set of 2 items measuring frequency and severity of each symptom A third item for SOB that asks how frequently the respondent has been forced to sleep sitting up or using at least three pillows was not used because internal consistency reliability was better with its elimination In preparation for this study, the internal consistency reliability of the fatigue and SOB symptom scales was tested in a separate sample of HF patients and found to be adequate with Cronbach's alpha values of 86 and 83 respectively In the current sample, the values were 88 and 89 respectively

Depression was measured with the 9-item Patient Health Questionnaire (PHQ-9), which offers a list of nine depressive symptoms with directions to indicate the frequency of each over the previous 2 weeks The time period was changed to 1 month in the parent study Response values are summed to create a range from 0 to 27 with higher scores indicating greater depression severity Content and construct validity have been established (Kroenke, Spitzer, & Williams, 2001, Muller-Tasch et al) The PHQ-9 has been used in patients with HF (Muller-Tasch et al , 2007, Riegel et al , 2006) Internal consistency reliability of the PHQ-9 has been demonstrated in samples of primary care patients and in women with Cronbach's alpha coefficients of 89 and 86 respectively (Kroenke et al) However, in this sample, internal consistency reliability of this measure was only 68

Statistical Analysis

Descriptive statistics were used to describe the sample and predictor and outcome variables Preliminary bivariate correlational analyses of all variables were conducted to verify expected relationships and identify potential multicollinearity Relationships between categorical predictors and OPH were assessed by statistical testing of differences between groups with independent *t*-tests or ANOVA To achieve aim 1, a hierarchical multiple regression analysis using five steps was performed with all variables in each block entered simultaneously The variables entered in each block are depicted in Figure 1 Interaction terms of age with each of the biophysiological variables and each of the functioning variables were included in the appropriate blocks based on empirical evidence of such effects (Aalto et al, 2006, Schnittker, 2005) Substantial multicollinearity was noted between the interaction terms and their associated individual variables Centering continuous variables to the mean and recomputing the interaction terms using the centered variables improved the collinearity statistics so that variable inflation factors were less than 5. All assumptions of linear ordinary least-squares regression were assessed and no violations were found.

To achieve aim 2, a multiple mediator analysis was conducted to assess the indirect effects of physical symptoms on OPH via one or both of the functional status variables. The bias-corrected bootstrapping method for multiple mediator analysis employing macros developed by Preacher and Hayes (2008) was used to test total and indirect effects in the model. This method reduces potential bias due to omitted variables and offers the advantage of determining the total indirect effect of symptoms on OPH as well as the unique indirect effects of each mediator, conditional on the presence of the other mediator in the model. Bootstrapping was conducted by nonparametric resampling with replacement in which subsamples of the dataset were repeatedly selected 1,000 times to conduct repeated estimations of the indirect effect and to create an empirical approximation of the sampling distribution of the effect with determination of the 97.5th and 2.5th percentiles to construct 95% confidence intervals. The bootstrap method does not require normality of the sampling distribution of the indirect effects and the calculated confidence intervals are more accurate than ordinary ones because they are not forced to be symmetrical, a factor that results in accuracies. Based on the findings of the regression analysis, a moderated mediation analysis was also conducted to assess whether gender moderated the mediation of SOB or fatigue by social functioning. The method recommended by Preacher, Rucker, and Hayes (2007) was used to compute conditional indirect effects in males and females. Significance level for all calculations was set at $P = .05$. Data were analyzed using SPSS 17.0 software (SPSS, Inc, Chicago, Illinois).

Results

Patient Characteristics

Descriptive statistics for the sample are provided in Table 1 Only 25 participants (9 4%) were without comorbid conditions The vast majority (76 2%) had a total of 3 or more chronic illnesses including their HF and over one-third (37 0%) had 5 or more Overall, the sample was moderately ill as classified by the Charlson Comorbidity Index Twenty-eight participants (10 6%) had multiple comorbid illnesses with an index score of 5 or more Descriptive statistics for OPH and the continuous predictors are provided in Table 2

More than half (55 1%) of the participants rated their OPH as fair or poor and only 11 3% rated their OPH as very good or excellent Most patients reported being symptomatic with fatigue (61 5%) or SOB (50 9%) at least weekly Only 11 3% of the sample experienced a worsening in symptoms during the previous month Most (55 1%) participants reported no or minimal depressive symptoms and the mean PHQ-9 score was below the threshold for even mild depression Most (64 2%) subjects reported no difficulty with life activities because of depressive symptoms The vast majority of participants reported limitations in physical functioning (88 3%) and social functioning (82 6%) due to HF

Bivariate Relationships

Correlational relationships between predictor variables and OPH are shown in Table 3 A strong association was evident between physical functioning and OPH while other predictors had weak to moderate correlations with OPH Age was not correlated with OPH Relationships between OPH and categorical variables are described with mean differences in Table 4

Regression Analysis

The results of the hierarchical regression analysis are summarized in Table 5 Age, gender, race/ethnicity, education, and income accounted for 22 4% of the variance in OPH, dropping to 20 5% after adjustment for the number of variables, $F(6,258)$ = 12 38, p < 001 Income, gender, and race/ethnicity were significant predictors of OPH in this model with higher income and female gender predicting better OPH and black compared to white race/ethnicity predicting worse OPH All variables were retained because of theoretical importance and collective contribution to variance explained

Several variables were not retained in each of the sequential models because they offered no significant information These included number of chronic illnesses, atrial fibrillation, and diabetes in the block with comorbid burden and all of the interaction terms involving age, with the exception of age by comorbid burden When physical and social functioning were added in the last step of the regression analysis, neither coefficient was significant (t = 1 72, P = 09 and t = 1 40, P = 16 respectively), but each was significant when the other was removed Based on changes in coefficient values for gender and black race/ethnicity when social functioning was removed, the addition of interaction terms for social functioning with each of these variables was tested in a model with both functioning variables included The gender by race/ethnicity interaction term offered no significant information and was not retained However with the gender by social functioning interaction term included, social functioning and the interaction term were both significant independent predictors of OPH in the final model Although, the coefficient for physical functioning was not significant (t = 1 68, P = 09) in this final step, the variable was retained because of theoretical importance

When controlling for individual characteristics, comorbid burden, significantly influenced by age, uniquely accounted for 6% of the variance in OPH. Adjusting for individual characteristics and comorbid burden, fatigue, SOB, and symptom stability were each significant independent predictors of OPH and explained an additional 10.5% of the variance in OPH. Depressive symptoms, when controlling for individual characteristics, comorbid burden, and physical symptoms, were a significant independent predictor of OPH, but explained only an additional 1% of the variance. Finally, when controlling for individual characteristics, physical functioning, social functioning, and a gender by social functioning interaction term explained an additional 3% of the variance in OPH beyond what was explained by all the other variables.

The final model containing 15 variables explained 39.2% of the variance in OPH after adjustment for the number of variables. Six variables were significant independent predictors of OPH: income, social functioning, comorbid burden, symptom stability, black versus white race/ethnicity and the interaction of gender and social functioning, the later indicating that social functioning was a stronger predictor for males than for females. Higher OPH was predicted by higher income, symptom stabilization or improvement, and, in males only, higher social functioning. When gender coding was reversed, social functioning was not a significant predictor in females. Lower OPH was predicted by higher comorbid burden and black as compared to white race/ethnicity. The other 9 variables collectively contributed to the explanation of the variance in OPH, significantly increasing the R^2 value, but none offered significant *unique* contributions. These included higher age, female gender, more education, lower fatigue burden, lower SOB burden, and higher physical functioning predicting higher OPH and depressive symptoms and other race/ethnicity compared to white predicting lower OPH The age by comorbid interaction term indicated that the negative association between comorbid burden and OPH was stronger among younger patients

As depicted in Figures 2 and 3, physical and social functioning mediated the effect of SOB ($F(3, 261) = 37\ 42$, $P <\ 001$) and fatigue on OPH ($F(3, 261) = 36\ 33$, $P <\ 001$) In both cases the total effect of symptoms on OPH was significant, but their direct effect on OPH was nonsignificant indicating total mediation of the effect of the physical symptom through the mediating variables In each model, the two indirect effects were not significantly different from each other indicating that both physical functioning and social functioning equally mediate the influence of the symptom on OPH In both instances, the mediation model accounted for 29% of the variance in OPH Gender did *not* moderate the mediation of the influence of SOB on OPH by social functioning as evidenced by a nonsignificant interaction effect ($B = -0\ 19$, $P =\ 07$) However, gender *did* moderate the mediation of the influence of fatigue on OPH by social functioning as evidenced by the interaction effect differing significantly from zero ($B = -0\ 22$, $P =\ 04$) The coefficient for the conditional indirect effect of fatigue on OPH mediated by social functioning for females was $B =\ 15$, $P =\ 02$, 95%CI [0 02, 0 28] and for males was $B =\ 30$, $p <\ 001$, 95% CI [0 20, 0 40] indicating that both were significant, but the strength of mediation was stronger for males than for females

Discussion

OPH is not only an indicator of current health, but a powerful predictor of adverse health outcomes including hospitalization, mortality, and low HRQOL Therefore, the purpose of this study was to determine the key variables associated with OPH in persons with chronic HF and to evaluate the amount of variability in OPH attributable to each We found that the selected variables collectively accounted for almost 40% of the variance in OPH Each group of variables uniquely explained a significant portion of the variance over and above variables already included in the model Six variables were significant independent predictors of OPH, one of which interacted with gender Physical and social functioning mediated the relationship between each of the physical symptoms and OPH The mediation of fatigue by social functioning was stronger for males than for females

Our finding that the selected variables accounted for 39 2% of the variance in OPH after adjustment for the number of variables is comparable to the 29% to 38% range reported in large populations studies (Aalto et al , 2006, Bailis et al , 2003, Bryant et al , 2000, Lewis & Riegel, 2010) In a study of older patients with a combination of comorbid conditions (Bayliss et al , 2007) and one study of HF patients (Sullivan et al 2007), 44 7% and 46% of the variance in OPH were explained respectively with similar predictors The higher value in the other HF study may have been due to the homogeneity of the primarily white, male sample which was limited to patients with advanced disease, minimal comorbidity, and potential for cardiac transplant (Sullivan) The specific variables that collectively predicted OPH in our study are consistent with those found in population studies (Bryant et al , Farmer & Ferraro, 1997, Schnittker, 2005, Shooshtari et al , 2007), although only one included a measure of physical symptoms (Shooshtari et al) and only one measured social functioning (Bailis et al) The contribution of symptoms and social functioning o the variance in OPH in our study is consistent with other studies of chronically ill patients (Aalto et al , Bayliss et al , Nguyen et al , 2008, Walke et al , 2007, Lewis & Riegel) Fatigue and SOB were also identified as predictors of OPH in two other studies of HF patients (Heo et al , 2005, Sullivan et al , 2007)

We found that the unmodifiable individual characteristics of age, gender, race/ethnicity, education, and income accounted for a substantially larger amount of the variance in OPH than the 5 3% found in a population study of community-dwelling individuals 60 years and older (Bryant, 2000) Our results also differ from those of Clark et al (2005) in which the same variables plus social-cognitive factors and social support explained only 14% of the variance in OPH in HF patients living in a low-income neighborhood The difference in these results may be related to the significance of income in our sample This predictor remained significant through all steps of the hierarchical regression and had the largest standardized coefficient of all variables in the final model Interestingly, 83 4% of our subjects reported having an income that was enough or more than enough to meet household needs Chronic illness is expensive and the financial income to obtain medical care, drug therapy, and assistance with lifestyle modification or personal obligations may offer protection for OPH from the added stress or lack of treatment created by inadequate resources Our sample also had a much higher prevalence of males than other studies examining the unique influence of this group of variables Income may influence OPH more in males than females In a sample of HF patients that was 91% male, Rosen and colleagues (1997) noted a direct relationship between family income and perceived health though income did not reach statistical significance

Our finding that each group of variables uniquely explained a small, but significant portion of the variance over and above those already added to the model is consistent with theoretical modeling of the integrative nature of this concept (Wilson & Cleary,1995, Ferrans et al , 2005) yet highlights the additional and distinct information each offers The single population study that conducted a similar type of analysis found similar results (Bryant et al , 2000) Ours are the first such results in patients with HF

The significant independent predictors of OPH in our sample, in addition to income, were Black race/ethnicity, comorbid burden, symptom stability, and social functioning in men only Our finding that Black race/ethnicity predicts a lower OPH is consistent with population studies, but a new finding in patients with HF Only one other study of OPH in HF patients had sufficient black subjects to analyze race and no association was found (Clark et al , 2005) The difference in results may lie in the fact that Black respondents in that study were likely to be female while in our sample most Black subjects were male Comorbidity has also been identified as a predictor of OPH in multiple population studies (Brown et al , 2005, Menec et al , 2007, Shooshtari et al , 2007, Bryant et al , 2000, Kosloski et al , 2005, Gerber et al , 2009, Lewis & Riegel, 2010) and one study of chronically ill subjects (Bayliss et al , 2007) Our findings are in contrast to the one HF study that included comorbidity and found no relationship with OPH , likely because billing codes were used to measure comorbidity (Clark et al) Only one other study included a measure of symptom stability In a lagged (time series) hierarchical regression analysis of data collected daily over 8 weeks in 54 residents of several retirement communities, Winter et al (2007) found that a change in symptoms, after controlling for level of symptoms, contributed independently to the variance in

OPH Our findings add to the empirical support for the importance of symptom change to OPH

Our finding that, in men only, social functioning was a significant independent predictor of OPH, stronger than physical functioning was unexpected To our knowledge, only one small study has reported such a relationship (Smith et al , 1999) Smith et al found similar results in a sample of 89 HIV positive men In all other studies and a meta-analysis of predictors of OPH, physical functioning is a far stronger predictor of OPH (Bayliss et al , 2007, Heo et al , 2007, Smith et al , Lewis & Riegel, 2010) It should be noted that the measure we used contains items conceptualized by others as both social and role functioning (Ware & Sherbourne, 1992) It may be a more inclusive measure and possibly more sensitive to the influence of ill health

We are the first to find that, in a sample of HF patients, physical and social functioning mediated the effects of SOB and of fatigue on OPH and the direct effect of physical symptoms was not significant when functional status was in the model Our results are in sharp contrast to that of Heo et al (2007) who found no mediation effect by functional status in the relationship between symptoms and OPH This difference is likely due to striking differences in the study samples as their subjects were patients hospitalized for acute decompensated HF Also, NYHA was used to measure functional status in Heo's study and no measure of social functioning was included Using both of the KCCQ subscales may provide a more inclusive, and possibly more sensitive, measure of functioning In patients with HIV, Sousa and Kwok (2006) also found that physical functioning mediated the effect of symptoms on OPH, but unlike us, also found a significant direct effect Our findings are consistent with the WCM model which postulates that symptoms influence OPH through their effect on functioning and help explain the mechanism of the relationship between symptoms and OPH To our knowledge, the gender moderation of the mediation effect of social functioning on the relationship between fatigue and OPH is also a new finding The mediation of fatigue by social functioning was stronger in men than in women, possibly due to lower social functioning scores in the males as compared to females, though the difference in mean scores was not significant It also may be that the restriction of social/role activities by fatigue is considered by males to be more indicative of ill health, consistent with Jylha's (2009) hypothesis that personal expectations influence health ratings

Limitations

Because we conducted a secondary analysis of data collected for the parent study, our study may have failed to consider other potential variables that may influence OPH in HF patients such as two factors identified in multiple previous studies, physical activity and a broader construct of mental health encompassing not only depression, but also affect and emotional distress Selection bias was possible because patients with low levels of OPH may have been more likely to refuse to participate when informed of the longitudinal nature and testing requirements of the parent study In this sample, internal consistency reliability of the PHQ-9 was unacceptably low and it may not have been a valid measure of depressive symptoms One of the items, fatigue, was a prevalent physical symptom of HF reported by most of our sample and another, inadequate sleep, is highly related to the symptom of excessive daytime sleepiness, one of the enrollment criteria for half of the sample in the parent study Finally, the use of cross-sectional data precludes establishment of a causal relationship between variables and may produce misleading results of mediation analyses

Conclusions and Implications

These results offer useful information for targeting vulnerable populations at risk for adverse outcomes and for guiding further assessment and tailoring interventions when OPH ratings are low The non-modifiable factors of black race, lower income, and higher comorbid burden identify at-risk patients and can be used to guide efficacious use of limited resources The particularly strong significance of income on OPH highlights the role of available resources in health perceptions and offers a challenging but potentially significant opportunity for creative nursing intervention

The failure to recognize worsening symptoms in HF patients is well known and poses a challenge for clinicians A guided assessment based on our results can be used to facilitate appraisal If OPH values decrease or are low, a focus on patient ability to function in life activities, especially social activities in men, with attention to a possible change in symptoms underlying any disability may facilitate recognition of a change in patient condition and provide direction for intervention before serious outcomes occur Finally, because we found that the mediation of fatigue by social functioning was stronger in men than in women, an increase in social functioning limitations in men, particularly, may herald worsening or profound fatigue, a symptom that may not be thought noteworthy by a patient but is associated with worsening HF and need for rehospitalization in patients with chronic HF (Albert, Trochelman, Li, & Lin, 2010, Friedman & Quinn, 2008) In summary, HF patients who are younger, male, black, with a lower formal education and income, higher comorbid burden, more physical symptoms, worsening symptoms, more depressive symptoms, and lower physical and social functioning have lower OPH

Our results also support the variables and theoretical relationships depicted in the study model, but with comorbid burden as a single biophysiological indicator Further research is necessary to identify other factors associated with the large amount of unexplained variance in OPH and to further explore gender differences, as well as age, ethnic, and cultural differences Longitudinal studies are needed to capture changes in OPH and its predictors over time in order to establish the temporal relationships required in casual modeling and mediation analyses A different measure of depressive symptoms in statistical modeling that also includes physical symptoms is needed to clarify the unique role of depression in OPH ratings We recommend the use of the CCI rather than a count of the number of chronic illnesses in future research because this measure was a stronger predictor of OPH even as other variables were added to the model

Numerous efforts have been made to improve outcomes for HF patients primarily in the form of evidence-based practice guidelines and disease management programs Although progress is being made, the prognosis for those with HF remains dismal and clinicians are continually challenged with the dilemma of how to improve the lives of these patients Armed with an understanding of the factors that influence OPH, clinicians can effectively intervene in patients with decreasing or low OPH and possibly lessen their risk for negative outcomes or at least delay those that are inevitable

What's New?

- In patients with chronic heart failure the individual characteristics of age, gender, race/ethnicity, education, and income along with comorbid burden collectively explained 26% of the variance in OPH, with lower income, black race, and higher comorbid burden significant independent predictors so these characteristics help identify patients at greatest risk for low OPH to target for intervention
- Physical symptoms, physical and social functioning, and, to a lesser extent, depressive symptoms collectively explain an additional 13 2% of the variance in OPH after controlling for individual characteristics and comorbidity and each offers a unique contribution
- A change in symptoms was a stronger predictor of OPH than symptom presence and severity and, in men only, social functioning was a stronger predictor of OPH than physical functioning
- Physical and social functioning mediated the effect of SOB and of fatigue on OPH and the mediation of fatigue by social functioning was stronger in men suggesting that a focus on ability to function in life activities is warranted if OPH is low or decreases

Table 1

Sample Characteristics (N = 265)

Variable	Mean (SD) or Number (%)
Age (range 24 to 89)	61 89 (12 40)
Male gender	170 (64 2)
Race/ethnicity	
White	164 (61 9)
Black	92 (34 7)
Other	9 (3 4)
Education level	
Less than high school	26 (9 8)
High school	95 (35 8)
Business school, some college, or associate degree	73 (27 5)
Bachelor's degree	43 (16 2)
Graduate degree	28 (10 5)
Household income	
Not enough	44 (16 6)
Enough	127 (47 9)
More than enough	94 (35 5)

Heart failure type	
Systolic	183 (69 1)
Diastolic	50 (18 9)
Mixed	32 (12 1)
Ejection fraction (n = 264)	35 25 (17 05)
Preserved ejection fraction (50% or greater) (n = 264)	62 (23 5)
Ischemic HF	98 (37 0)
Mean duration of HF in months	74 71 (72 29)
New York Heart Association Class	
I	12 (4 5)
II	45 (17 0)
III	158 (59 6)
IV	50 (18 9)
Comorbid conditions	
Hypertension	169 (63 8)
Atrial fibrillation	86 (32 5)
Diabetes	103 (38 9)
CAD (history of myocardial infarction)	98 (37 0)
Renal disease	70 (26 4)
Chronic obstructive pulmonary disease	58 (21 9)
Pulmonary hypertension	54 (20 4)
Anemia	49 (18 5)

Cerebrovascular dısease	39 (14 7)
Perıpheral vascular dısease	31 (11 7)
Cancer	19 (7 2)
Connectıve tıssue dısease	14 (5 3)
Lıver dısease	3 (1 1)
AIDS	1 (0 4)

Note Data gıven as mean (SD) or number (%). CAD = coronary artery dısease

Table 2

Descriptive Statistics for Continuous Variables (N = 265)

Variable	**Range**	**Mean (SD)**
Number of chronic illnesses	1-10	4 00 (1 88)
Charlson Comorbidity Index	1-11	2 77 (1 66)
Fatigue symptom Score [a]	0-100	61 89 (29 55)
Shortness of breath symptom score [a]	0-100	67 56 (29 64)
Symptom stability score [a]	0-100	57 26 (22 33)
Depressive symptoms score	0-18	4 48 (3 66)
Physical functioning score [a]	0-100	68 93 (23 55)
Social functioning score [a]	0-100	65 79 (28 16)
Overall perceived health [a]	0-100	40 68 (26 68)

[a] higher score indicates better health

Table 3

Intercorrelations between Overall Perceived Health and Predictor Variables

	Age	Education	Income	# CI	CCI	Fatigue	SOB	Symptom Stability	Depressive Symptoms	Physical Function	Social Function
OPH	07	25***	39***	- 27***	- 27***	38***	45***	18**	- 32***	51***	49***
Age	-	- 11	18**	34***	25***	22***	08	08	- 18**	- 01	12
Education		-	28***	- 16**	- 10	04	18**	- 00	- 12*	21**	13*
Income			-	- 08	- 02	28***	33***	- 04	- 17**	38***	37***
# CI				-	71***	- 00	- 16**	03	01	- 28***	- 16**
CCI					-	- 05	- 16*	04	04	- 22***	- 16*
Fatigue						-	60***	15*	- 54***	54***	68***
SOB							-	22***	- 40***	68***	65***
Symptom Stability								-	- 14*	16**	14*
Depressive Symptoms									-	- 38***	- 42***
Physical Function										-	71***

Note Values for educatıon and ıncome are reported as Spearman's rho, all other values reported as Pearson's r correlatıon coefficıent

CI = number chronıc ıllnesses, CCI = Charlson Comorbıdıty Index, Fıb = fibrıllatıon, OPH = overall perceıved health, SOB = shortness of breath *p < 05 **p < 01 ***p < 01

Table 4

Relationships between Overall Perceived Health and Categorical Variables (N = 265)

Variable	Mean OPH (SD)	Test Statistic$_{df}$	p	95% CI
Gender		$t_{263} = -1\ 59$	11	[-12 14, 1 28]
Males	38 73 (27 24)			
Females	44 16 (25 41)			
Race/Ethnicity[a]		$F_{2,262} = 15\ 58$	< 001	
White	47 47 (26 12)			
Black	29 32 (24 51)			
Other	33 00 (15 87)			
Education		$t_{263} = -5\ 01$	< 001	[-24 73, -10 78]
Bachelor's or Graduate Degree	53 68 (26 41)			
Less than Bachelor's Degree	35 92 (25 21)			
Household income[b]		$F_{2,262} = 26\ 16$	< 001	
Not enough	26 95 (24 36)			
Enough	34 95 (24 78)			
More than enough	54 83 (24 02)			
Diabetes		$t_{247} = 3\ 51$	001	[4 87,17 29]
Yes	33 90 (22 90)			

No	44 98 (28 05)			
Atrial fibrillation		t_{263} = 91	37	[-3 73, 10 06]
Yes	38 53 (26 84)			
No	41 70 (26 61)			

[a]Post hoc testing using Bonferroni correction revealed a significant difference between the white and black groups (p < 001, 95% CI [10 21, 26 10]) [b] Post hoc testing using Bonferroni correction revealed a significant difference between those with more than enough to make ends meet and those with enough (p < 001, 95% CI [11 86, 27 89]) as well as those without enough to make ends meet (p < 001, 95% CI [17 12, 38 64])

Table 5

Coefficient values for each predictor from hierarchical regression analysis

	Step									
	1		2		3		4		5	
Predictor	*B*	*β*	*B*	*β*	*B*	*β*	*B*	*β*	*B*	*β*
Age	06	03	21	10	10	04	07	03	12	05
Gender	7 08	13*	5 07	09	5 82	11*	6 36	12*	5 70	10
Black versus white	-11 02	- 20**	-8 30	- 15*	-6 92	- 12*	-7 22	- 13*	-6 39	- 11*
Other race/ethnicity versus white	-10 45	- 07	-9 08	- 06	-5 03	- 03	-5 48	- 04	-4 48	- 03
Education	2 42	10	2 45	11	2 17	09	1 84	08	1 67	07
Income	11 52	30***	11 85	31***	9 09	24***	9 28	24***	7 87	21***
Comorbid burden			-4 16	- 26***	-3 47	- 22***	-3 44	- 21***	-2 99	- 19**
Age x comorbid burden			17	12*	14	10*	15	11*	10	07
Fatigue[a]					14	15*	08	09	02	02
SOB[a]					15	17*	14	16*	04	05

Symptom stability[a]					17	14*	16	14*	15	12*
Depressive symptoms							-9 10	- 12*	- 83	- 11
Physical functioning[a]									15	14
Social functioning[a]									18	20*
Gender x social functioning									- 20	- 12*
Adjusted R^2		20***		26***		36***		37***		39***
ΔR^2				06***		10***		01*		03**

Note Gender coding was 0 for males and 1 for females β = standardized regression coefficient, SOB = shortness of breath, Δ= change [a]higher score indicates better health $*p <$ 05 $**p <$ 01 $***p <$ 01

Figure Legends

Figure 1 Study Model

Figure 2 Multiple mediation model of shortness of breath on OPH through physical and social functioning with coefficients indicated for each path Total effect = 41 (p < 001) Indirect effect for physical functioning = 16 (95% CI [05, 26]) and for social functioning = 14 (95% CI [03- 23]) Contrast in indirect effects was 0 03 (95% CI [- 15, 20]) R^2 = 30, Adjusted R^2 = 29 ($F_{3,261}$ = 37 42, p < 001)

** < 01 *** < 001

Figure 3 Multiple mediation model of fatigue on OPH through physical and social functioning with coefficients indicated for each path Total effect = 34 (p < 001) Indirect effect for physical functioning = 15 (95% CI [07, 23]) and for social functioning = 15 (95% CI [04, 25]) Contrast in indirect effects was 0 002 (95% CI, - 16, 17) R^2 = 29, Adjusted R^2 = 29 ($F_{3,261}$ = 36 33, p < 001)

** p < 01 *** p < 001

Predictor Variables

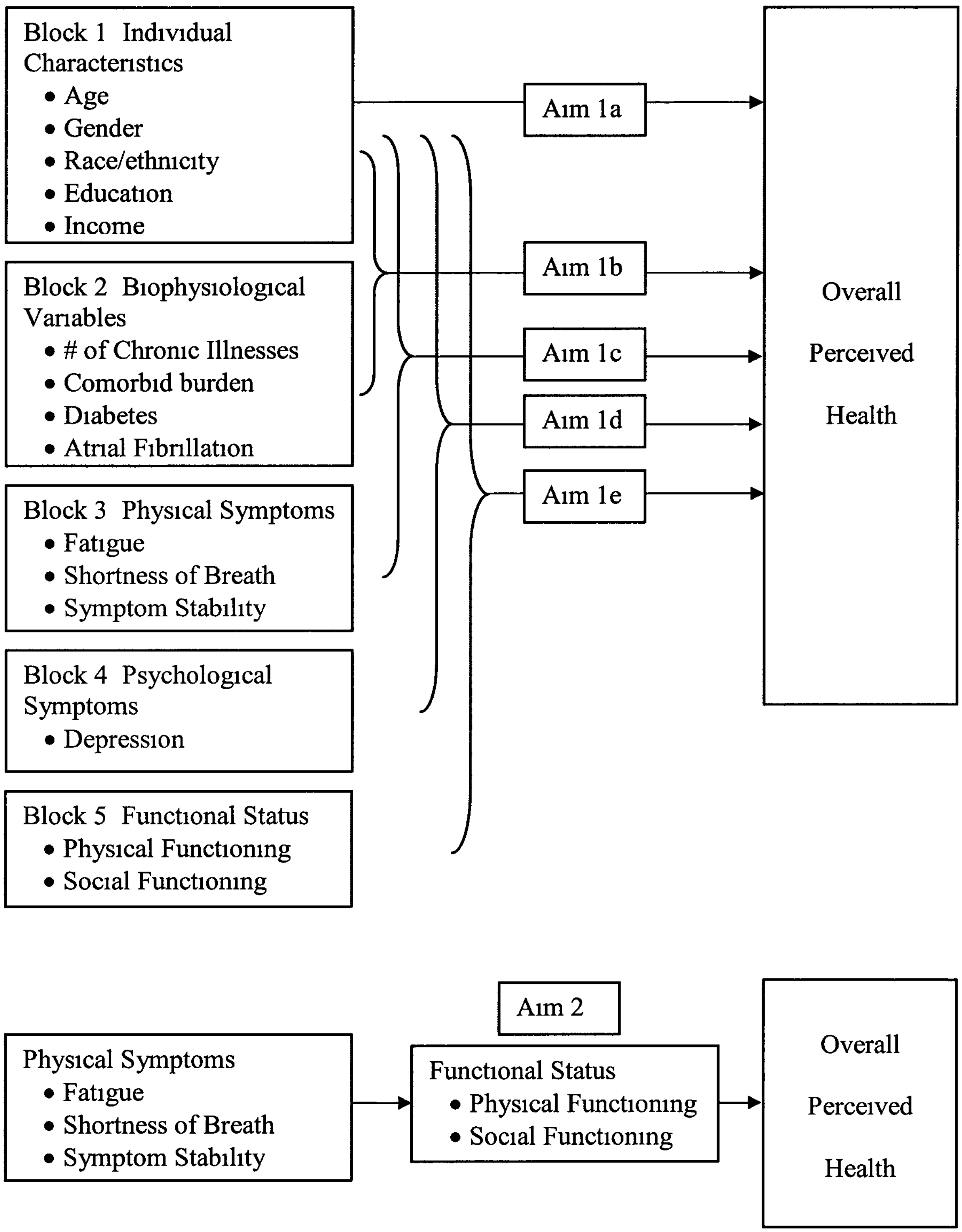
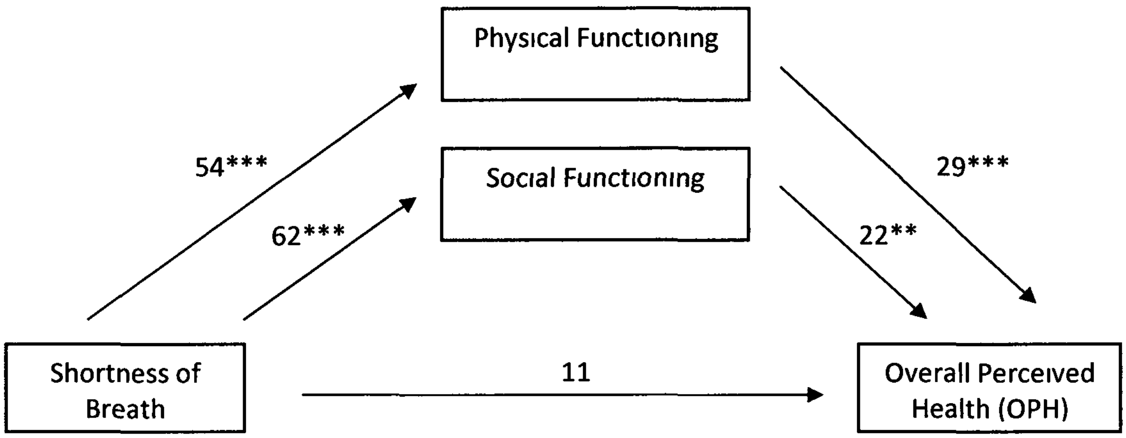


Figure 1 Study model



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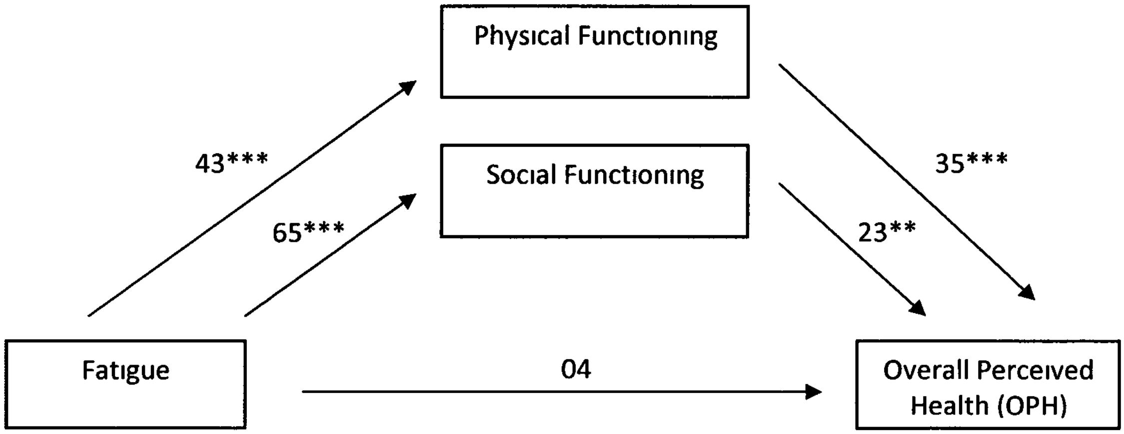

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Appendix

Outcomes Related to Low Overall Perceived Health

Reference	Sample	Mortality	Hospitali-zation	Resource Use/ Expenditure	Combination end-point	Functional Status	Other
Benyamini & Idler, 1999	Pop	X					
Biddiss, Brownsell, & Hawley, 2009	HF				X (Death, admission, immediate medical attention, medication change, advice)		
Boot, Heijmans, van der Gulden, & Rijken, 2008							X Work disability
Chipperfield, 1993	Pop	X					
Deeg & Kriegsman, 2003	Pop	X In age adjusted model					

Reference	Sample	Mortality	Hospitali-zation	Resource Use/ Expenditure	Combination end-point	Functional Status	Other
DeSalvo, Bloser, Reynolds, He, & Muntner, 2005	Cohort	X (after adjustment for FS, depression, comorbidity					
DeSalvo, Fan, McDonell, & Fihn, 2005	Primary Care Pts	X	X	X Outpatient use			
DeSalvo et al , 2009	pop			X Expenditures			
Diehr, Williamson, Patrick, Bild, & Burke, 2001	Pop	X					
Dowd & Zajacova, 2007	Pop	X					
Farkas, Nabb, Zaletel-Kragelj, Cleland, & Lainscak, 2009	HF	X					
Farmer & Ferraro, 1997	Pop					X Disability	X Psychological distress

Reference	Sample	Mortality	Hospitali-zation	Resource Use/ Expenditure	Combination end-point	Functional Status	Other
Frank-Stromborg, Pender, Walker, & Sechrist, 1990	Cancer						X Health promoting lifestyle
Fried, et al , 1998	Pop	X					
Gerber, Benyamini, Goldbourt, & Drory, 2009	AMI	X					
Gold, Franks, & Erickson , 1996	Pop	X	X				
Havranek et al , 2001	HF				X (mortality, HF ED visit, all-cause ED visit, HF hosp)		
Heo, Moser, Lennie, Zambroski, & Chung, 2007	HF						X HRQOL
Heo, Moser, Riegel, Hall, & Christman, 2005	HF						X HRQOL
Idler & Angel, 1990	Pop	X					

Reference	Sample	Mortality	Hospitali-zation	Resource Use/ Expenditure	Combination end-point	Functional Status	Other
Idler & Benyamini, 1997	Pop	X					
Idler & Kasl, 1991	Pop	X					
Jansky, Lekander, Blom, Georgiades, & Ahnve, 2005	Heart						X Vital exhaustion (IL-6)
Johansson, Brostrom, Dahlstrom, Alehagen, 2008	HF	X (CV)					
Jylha, Colpato, & Guralnik, 2006	Pop	X					
Kamphuis, et al 2009	Pop	X (CV)					
Kennedy, Kasl, & Vaccarino, 2001	Pop		X				
Konstam, et al , 1996	HF	X	X (HF)				
Kosloski, Stull, Kercher, & Van Dussen, 2005	Pop						X Depressive symptoms
Lee, et al , 2007	Pop	X					

Reference	Sample	Mortality	Hospitali-zation	Resource Use/ Expenditure	Combination end-point	Functional Status	Other
Luppa et al , 2010	Elderly			X Nursing Home Placement			
Mason, Katzmarzyk, Craig, & Gauvin, 2007	Pop	X					
McEwen, 2009	Diabetes	X					
Mossey & Shapiro, 1982	Pop	X					
Roe-Prior, 2004	HF		X	X (total hosp, MD visits, ED visits)			
Ruthig & Chipperfield, 2007	Pop		X	X LOS		X (functional well-being)	
Sebern, & Riegel, 2009	dyads of HF pts & caregivers						X Shared care
Sousa & Kwok, 2006	HIV						X HRQOL
Stuck, 1999	Lit review					X	
Stull, Kercher, & Kosloski, 1996	Elderly			X MD Visits			

Reference	Sample	Mortality	Hospitali-zation	Resource Use/ Expenditure	Combination end-point	Functional Status	Other
Sulllivan, Levy, Russo, Crane, & Spertus, 2007	HF				X Mortality or transplant		
Thong et al , 2008	Dialysis	X					
Tobiasz-Adamczyk, Brzyski, & Kopacz, 2008	Pop	X					
Weinberger et al , 1986	Pop	X		X Nursing Home Placement			
Wolinsky, & Tierney, 1998	Primary Care Pts						Expectations of hospitalizatio n & mortality
Wolinsky, Culler, Callahan, & Hohnson, 1994	Pop		X	X LOS & charges			
Wolinsky, Stump, Clark, 1995	Pop						X Physical activity & exercise
Wong, Wong, & Caplan, 2007	ED	X				X	

Reference	Sample	Mortality	Hospitali-zation	Resource Use/ Expenditure	Combination end-point	Functional Status	Other
Zimmermann, Ekholm, Grønbæk, & Curtis, 2008	Pop						X Physical activity

Note HF = heart failure, pop = population, FS = functional status, AMI = acute myocardial infarction, ED = emergency department, hosp = hospitalization, HRQOL = health-related quality of life, CV = cardiovascular, MD = medical doctor, LOS = length of stay