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An Evaluation of Hypertension Control in the US Population and Patient-Reported Outcomes in a Clinical Trial of Heart Failure

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An Evaluation of Hypertension Control in the US Population and Patient-Reported Outcomes in a Clinical Trial of Heart Failure

A dissertation submitted in partial satisfaction of the requirements for the degree Doctor of Philosophy in Health Policy and Management

by

John Michael Dinkler

2016

ABSTRACT OF THE DISSERTATION

An Evaluation of Hypertension Control in the US Population and Patient-Reported Outcomes in a Clinical Trial of Heart Failure

by

John Michael Dinkler

Doctor of Philosophy in Health Policy and Management

University of California, Los Angeles, 2016

Professor Michael K. Ong, Co-chair

Professor Carol M. Mangione, Co-Chair

Background:

The morbidity, mortality and costs associated with hypertension and heart failure in the US are enormous. In the US population, the positive role of having a usual source of care (USOC) on the receipt of preventative services is known. However, associations between USOC and hypertension control and whether a differential association across age groups exists is unknown in the US population.

Heart failure affects patients in myriad ways: economically, physically, socially and emotionally. Heart failure negatively impacts health-related quality of life (HRQOL), but age-related differences in HRQOL (and specifically emotional health) are unknown. Finally, studies are mixed on whether increased monitoring and nurse coaching can impact emotional health post-discharge in recently hospitalized heart failure patients.

Methods:

To assess the relationship between USOC and hypertension control, I use data from the National Health and Nutrition Examination Survey (NHANES) from 2007-2012. I utilize multivariable logistic regression to evaluate the association between having a USOC and hypertension control. The differential effect of USOC on hypertension control by age is assessed using predicted marginal effects for various age groups within this model and then analyzing pairwise comparisons of the marginal effects.

To examine age-related differences in emotional health in recently hospitalized heart failure patients, I analyze longitudinal data from the BEAT-HF study—a multicenter trial comparing the impact of wireless remote monitoring and nurse coaching versus usual care on emotional health for patients hospitalized with heart failure. Multivariable linear regression and mixed effects models are utilized to evaluate whether there are baseline and longitudinal differences in emotional health across age groups. To analyze whether the association between age and emotional health outcomes is mediated by physical health and/or social health I use a multi-step regression model allowing for cross-equation error correlation ("seemingly unrelated regression") and structural equation modeling. To assess the intervention effect on emotional health in the study, I utilize mixed effects linear regression controlling for treatment arm and hospital level random effects.

Results:

In adjusted analyses, those with a USOC had a higher odds of hypertension control [OR=3.89, 95%CI (2.15-6.98)]. The marginal effect of having a USOC is associated with a 30 percentage-point higher probability of controlled blood pressure compared to those without a USOC [marginal difference in probability=0.30, 95%CI (0.19-0.41)]. In tests of pairwise comparisons of marginal effects, there was a 7-8 percentage point difference in marginal effect of USOC on hypertension control in the youngest group (compared to all middle age groups) which was statistically significantly lower. In terms of the US population this difference amounts to 70,000-80,000 fewer young individuals with controlled hypertension per million individuals with hypertension. There was also a 3-4 percentage point difference in marginal effect in the oldest age group (compared to all middle age groups) which was statistically significantly lower. This difference amounts to 30,000-40,000 fewer older individuals with controlled hypertension per million in the US hypertension population.

In the BEAT-HF trial, older individuals had better emotional health in multivariable linear regression models controlling for demographic and clinical characteristics [lower scores indicating better emotional health; β=-1.9, 95% CI (-3, -0.8)]. The effect of age on emotional health was partially mediated by physical health in all models ("seemingly unrelated regression" with simultaneous regression equations and structural equation modeling). The mixed effects analysis for the intervention's effect on emotional health showed a small but statistically significant effect at 180 days [β=-1.3, 95%CI(-2.2, -0.02)]. By Cohen's rules of thumb, the standardized difference in groups approaches a "small" effect size (adjusted effect size(ES)=0.17 vs. "small" ES=0.2), but is below it. In mixed effects models using tests of interaction, there was no differential effect of treatment by age or social isolation.

Conclusion:

Having a usual source of care is significantly associated with improved hypertension control in the US population. The variation in the association across age groups has important implications in targeting age-specific anti-hypertensive strategies to reduce the burden of hypertension in the US population.

Older patients with heart failure in this study have better emotional health than younger patients. This may be related to increased coping or acceptance of limitations, since older patients overall had more comorbidities and a higher proportion of NYHA class III heart failure. Both treatment and control groups had improved emotional health scores in the post-discharge period, but the telemonitoring and nurse coaching intervention had small positive effects on emotional health at 180 days. Treatment non-adherence may have minimized the effect on emotional health, but this large-scale randomized controlled trial likely gives an accurate assessment of the real-world effect of telemonitoring and nurse coaching on a broad heart failure population.

The dissertation of John Michael Dinkler is approved.

Ronald D. Hays

Jack Needleman

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University of California, Los Angeles

2016

Dedication

To my wife, Michal Beth: you are my strong, brilliant anchor. Thank you for your unwavering love and support in my academic journey. And to my children, Alethea and Daelen: your joy and energy makes the journey more fulfilling.

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Acknowledgements

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Biographical sketch

John Dinkler received his B.S. in Biology in 1999, graduating with highest honors from the University of California, Davis. He then went onto medical training at Boston University School of Medicine, finishing his M.D. summa cum laude in 2008. John trained in Internal Medicine at Brigham and Women’s Hospital in Boston, Massachusetts. He joined the UCLA Cardiology Specialized Training and Research (STAR) Fellowship Program in July 2011. He has published three review articles examining the ACC/AHA Cholesterol guidelines for various populations.

Introduction to the dissertation

This dissertation focuses on structural access to care and hypertension control in the US population and patient-reported outcomes in a heart failure clinical trial. The two diseases are major public health problems and are pathophysiologically linked. The American College of Cardiology and the American Heart Association staging system highlights the importance of hypertension in the development of heart failure by denoting the mere *presence* of hypertension as “Stage A” heart failure, despite a lack of symptoms. Hypertension is a key upstream factor that leads to left ventricular hypertrophy or *asymptomatic* left ventricular dysfunction (stage B) and eventual *symptomatic* left ventricular dysfunction (stages C/D, where stage D is advanced end-stage heart failure requiring specialized strategies like transplantation). Hypertension and heart failure make up a large proportion of the burden of cardiovascular disease in the U.S. population. An astounding 1 in 3 adults in the United States has hypertension, with estimated total (direct and indirect) costs estimated to be $46 billion.[1] 5.1 million Americans have heart failure, with 3 out of 4 heart failure patients having had antecedent hypertension. The mortality burden of heart failure remains high as well: half of cases will die within 5 years. [2,3] Beyond the mortality burden, the economic costs of heart failure are estimated at $31 billion and are expected to rise to over $70 billion by 2030.[1] With the aging baby boomer population and high prevalence of risk factors—smoking, obesity, hyperlipidemia, diabetes and hypertension—cardiovascular disease will remain one of the preeminent public health concerns in the future. [1,4,5,6,7]

In this dissertation hypertension and heart failure will be analyzed from different perspectives: hypertension through the population lens and heart failure through the patient’s perspective and experience. Beyond the clinical link, this dissertation is aimed at understanding the potential role of age in hypertension control and patient-reported outcomes (PROs) in heart failure. The reasons for potential age-related differences in outcomes likely encompass many dynamic factors: changing access to care, perceptions of illness, changing social support, ability for self-care, and comorbid burden.[8–10]

In Chapter One of the dissertation, I examine the role that structural access to care has on the control of hypertension in the United States and the potential modifying effect of age on the association. Chapter Two explores the association between age and emotional health in heart failure patients in a large clinical trial and how social isolation and physical health may mediate the association between age and emotional health. Finally, in Chapter Three I will focus on the effect of remote monitoring and nurse coaching on emotional health in heart failure patients and—again—the potential modifying role that age may play.

Chapter 1

Does Age Matter? Evaluating the Association between Usual Source of Care and Hypertension Control in the US Population: Data from NHANES 2007-2012

Background

Approximately 80 million US adults have hypertension with just over half controlled.[1] Because hypertension is a major risk factor for the development of heart failure, stroke and coronary artery disease, controlling hypertension is critical for reducing morbidity, mortality and health care costs.[5,7,11,12]

The burden of hypertension in older Americans is particularly striking. Nearly 3 out of 4 individuals >74 years old have hypertension and with each decade of life the stroke mortality rate escalates for those with hypertension compared to those with normal blood pressure.[5,12–14]

Elucidating the impact of having access to a usual source of care (USOC) on hypertension control has important policy implications in the organization of care and management of chronic disease. Observational studies have examined the association between having a USOC and the receipt of preventative care and found positive associations between regular sources of care and mammograms, flu vaccination, cholesterol checks, and blood pressure checks.[15–18]

Beyond blood pressure *checks*, there are few studies that have examined the relationship between structural access to care (i.e., insurance or a USOC) and *treatment* or *control* of blood pressure.[19,20] An older study using NHANES III data from the late 1980s and early 1990s found that having private health insurance and using the same facility or provider for health care was associated with higher odds of blood pressure control.[19] In another study, having a usual source of care was associated with a higher prevalence of *treatment* for hypertension in adults, but hypertension control was not examined.[20]

Given major changes in the treatment landscape and population demographics over the past 25 years, it is important to examine the relationship between structural access to care and hypertension control. Thus, this study has three major objectives: (1) to evaluate whether having a USOC is associated with hypertension control in the US population, (2) to evaluate whether the effect of USOC on hypertension varies by age group (3) to analyze age group behaviors (e.g., smoking, follow-up with providers, medication use) and USOC type utilization (e.g., traditional source of care, emergency department or none). Assessing the link between USOC and hypertension control, and differences in the association by age, is an important step in understanding what effect increasing structural access to care may have on the US hypertensive population.

Methods and Measures

Data Source

This cross-sectional study uses health interview and medical exam data from the National Health and Nutrition Examination Survey (NHANES) from 2007-2012. NHANES uses a complex, multistage sampling design to select a representative sample of the civilian non-institutionalized population in the US.[21] It is conducted in 2-year cycles by the National Center for Health Statistics (NCHS). The physical exam component contains data on blood pressure, height and weight that is gathered at a mobile exam center (MEC). In addition, the NHANES questionnaires assess comorbidities, self-reported health status, health habits, and information on USOC.

The NHANES sample for this study is restricted to the hypertensive population (i.e., those who are currently taking blood pressure medication or had systolic blood pressure 140 or diastolic 90 at the time of the mobile exam component). This restricted sub-sample is consistent with other studies assessing hypertension outcomes.[19,20]

Measures

Trained professionals measured blood pressure using sphygmomanometry and appropriately sized arm cuffs after 5 minutes seated rest. Blood pressure measurements were taken three consecutive times and the last two measurements were averaged together.[21]

"Hypertension control" is defined as average systolic blood pressure less than 140mmHg and diastolic less than 90mmHg.[5] Newer JNC8 criteria, which increases the systolic blood pressure target in older individuals, were not used because clinicians during the time period of this study would not have been using the new targets for the older population.[12] Treatment for hypertension was defined by one's response to the question: "Are you taking blood pressure medication?"

NHANES defines USOC as a place to go when one is ill and needs care; places are listed as hospital outpatient department, outpatient clinic or doctor's office, emergency department, or none.[22] For analyses looking at the proportion of blood pressure control in the US population, USOC type is classified as "traditional" USOC (clinic, doctor's office, or outpatient hospital department), emergency department USOC, and no USOC. For multivariate models and marginal effects analyses (see below) USOC is dichotomized to "traditional USOC" vs. "no USOC" (if individuals use the emergency department they are treated as "no USOC").

Other variables and their construction are as follows:

- The sample is restricted to adults 18 years of age and older and stratified by 10-year intervals to create six separate age-groups.
- Race/ethnicity is categorized as Hispanic, non-Hispanic White, non-Hispanic Black, and "other race" which includes multi-racial.

- Married individuals and those living with a partner are designated "married" and all others are treated as "not married."
- Insurance status is categorized as either insured or uninsured.
- Education is operationalized in terms of the highest level completed and is collapsed into three categories: (1) those that did not complete high school, (2) high school graduates and (3) college graduates.
- Income is categorized as family income in relationship to federal poverty level (FPL). Specifically, we create 4 mutually exclusive groups: (1) "Poorest"/<150%FPL, (2) 150-249% FPL, (3) 250-349% FPL, (4) >350% FPL.
- Self-reported health is categorized as *fair, poor, good, very good* or *excellent* health.
- Self-reported activity is categorized by whether or not individuals met the American College of Sports Medicine guidelines for aerobic physical activity.[23]
- Smoking is defined as smoking at least 100 cigarettes in one's lifetime.[24]
- Comorbidities such as diabetes, heart failure, prior heart attack (MI), prior stroke (CVA), and high cholesterol are all defined based on a patient's answers to the following question: "Has a doctor ever told you that you have/had 'X'?"
- Body mass index is calculated during the Mobile Exam Component and is defined as a person's weight (in kg) divided by their height (in meters) squared. We use the CDC definitions for underweight (BMI<18.5), normal weight (BMI 18.5 to 24.9), overweight (BMI 25-29.9) and obese (BMI 30 and above).

Study design and statistical methods

I use survey methods for all weighted bivariate analyses and regression models. Bivariate relationships between covariates (all of which are categorical) and USOC and bivariate associations between covariates and hypertension control are assessed using the chi-square test. I also examine bivariate relationships between the oldest age group (compared to all younger) and the youngest age group (compared to all older) with regard to anti-hypertensive medication use, frequency of follow up with medical care, smoking status, and exercise. Unadjusted weighted proportions of controlled hypertension are presented by USOC type (e.g., “traditional” USOC, Emergency Department, and none) and unadjusted weighted proportions of age groups are presented by USOC type. In multivariate logistic models USOC is treated as dichotomous (“traditional USOC” vs “no USOC”, where the emergency department is “no USOC”). I employ two logistic models to analyze the effects of USOC on hypertension control. The first adjusts for demographics and comorbidities and the second adjusts for demographics and comorbidities after imputation of variables with missing data (see below for missing data methods). Given lack of differential missingness by outcome group the primary model is the logistic model without imputation. I test the potential age-related differential association between USOC and hypertension control by examining the marginal effects of USOC on the probability of hypertension control at each age group and testing pairwise comparisons.[25] Predictions are generated using average probabilities among actual persons in the data and errors are weighted to account for population sampling.

Missing data

Variables with missing data are filled in via multiple imputation with chained equations using variables with complete data (age, gender, race/ethnicity, diabetes status, smoking status, USOC, and hypertension control).[26–28] I create five multiply imputed datasets and variables are tested in logistic models to ensure they are missing at random (MAR) .[29] Results are then aggregated across the imputed data sets to properly account for between imputation variance. Most of the variables have either no missing data or are missing <2%. Only three variables are missing approximately 10% (BMI category, income and hyperlipidemia).

Results

Bivariate analysis

In bivariate analyses those *without* a USOC are more likely to be younger, of Hispanic ethnicity or non-Hispanic black, and male. In addition, individuals *without* a USOC are less likely to be married, have insurance, have completed high school, and less likely to report having diabetes, heart failure, prior stroke or high cholesterol. A higher proportion of anti-hypertensive medication use and control is seen in those with a USOC (see Table 1.1).

Table 1.1 Characteristics of the NHANES 2007-2012 Adult Hypertension subsample by USOC

Total sample size n= 7,653 representing 87,298,349 individuals

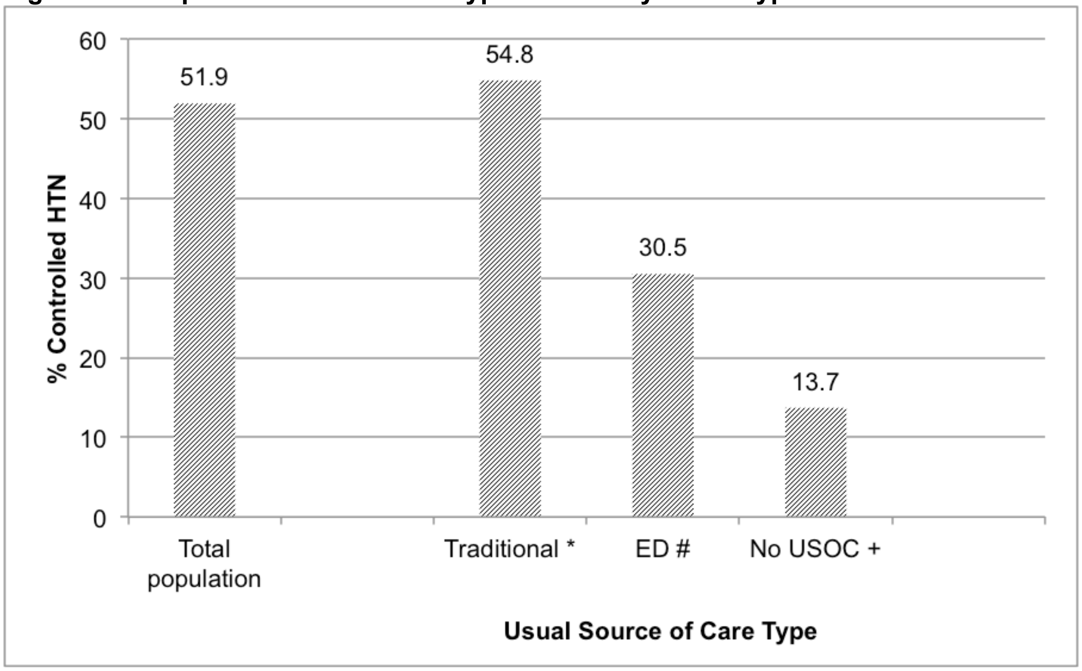
	USOC (n=6785)	No USOC (n=868)
	Weighted %=90.7 %	***Weighted % =9.3 %***
Age strata, no. (weighted %)		
18-34	504 (7.5%)	226 (28.5%)**
35-44	625 (11.4%)	145 (17.9%)**
45-54	1012 (19.3%)	186 (26.6%)**
55-64	1540 (24.4%)	167(15.5%)**
65-74	1523 (19.2%)	89 (7.1%)**
>75	1581 (18.2%)	55 (4.3%)**
Race/ethnicity, no. (weighted %)		
Hispanic	1359 (8.4%)	327 (23.1%)**
Non-Hispanic White	3159 (71.9%)	244 (48.9%)**
Non-Hispanic Black	1789 (14%)	228 (19.6%)**
Other race	478 (5.6%)	69 (8.4%)
Gender		
Male, no. (weighted %)	3158 (45.7%)	539 (65%)**
Marital status		
Married or partner, no. (weighted %)	3833 (63.7%)	430 (51.9%)**
Insurance status		
Insured, no. (weighted %)	6028 (90.9%)	385 (47.5%)**
Education, no. (weighted %)		
Less than high school	2110 (21.3%)	387 (34.5%)**
High school graduate or some college	3415 (54.2%)	390 (51.8%)
College graduate	1243 (24.5%)	90 (13.7%)**
Physical activity, no. (weighted %)		
Meeting physical activity guidelines	2262 (37.3%)	418 (51.5%)**
Smoking status, no. (weighted %)		

Non-smoker	3589 (52.8%)	441 (46.2%)*
Current smoker	1098 (15.4%)	274 (35.8%)**
Former smoker	2098 (31.8%)	153 (18%)**
Comorbidities, no. (weighted %)		
Diabetes	1558 (19%)	71 (6.3%)**
Heart failure	452 (5.7%)	18 (1.3%)**
Prior MI	522 (6.5%)	35 (3.2%)**
Prior stroke	549 (6.6%)	26 (2%)**
Hyperlipidemia	3218 (52.6%)	169 (33.2%)**
COPD	435 (6.6%)	26 (3.2%)*
BMI category, no. (weighted %)		
Obese	2848 (46.7%)	295 (41.9%)
Overweight	1968 (32.8%)	237 (30.7%)
Normal Weight	1220 (19.2%)	164 (24.7%)*
Underweight	74 (1.3%)	19 (2.7%)**
Hypertension treatment and control		
Taking anti-hypertensive medication, no. (weighted %)	4746 (70.7%)	182 (20.1%)**
Hypertension controlled, no. (weighted %)	2836 (54.8%)	97 (17%)**

*Statistically significant at p<0.05
**Statistically significant at p<0.01

Figure 1.1 illustrates the proportion of controlled hypertension by USOC type. Fifty-two percent have controlled hypertension. Only 14% without a USOC have controlled hypertension, compared to 55% with a traditional USOC (p<0.01). Those who use the emergency department as their USOC are less likely to have controlled hypertension than those with a “traditional” USOC (31% vs. 55%, p<0.01).

Figure 1.1 Proportion of controlled hypertension by USOC type



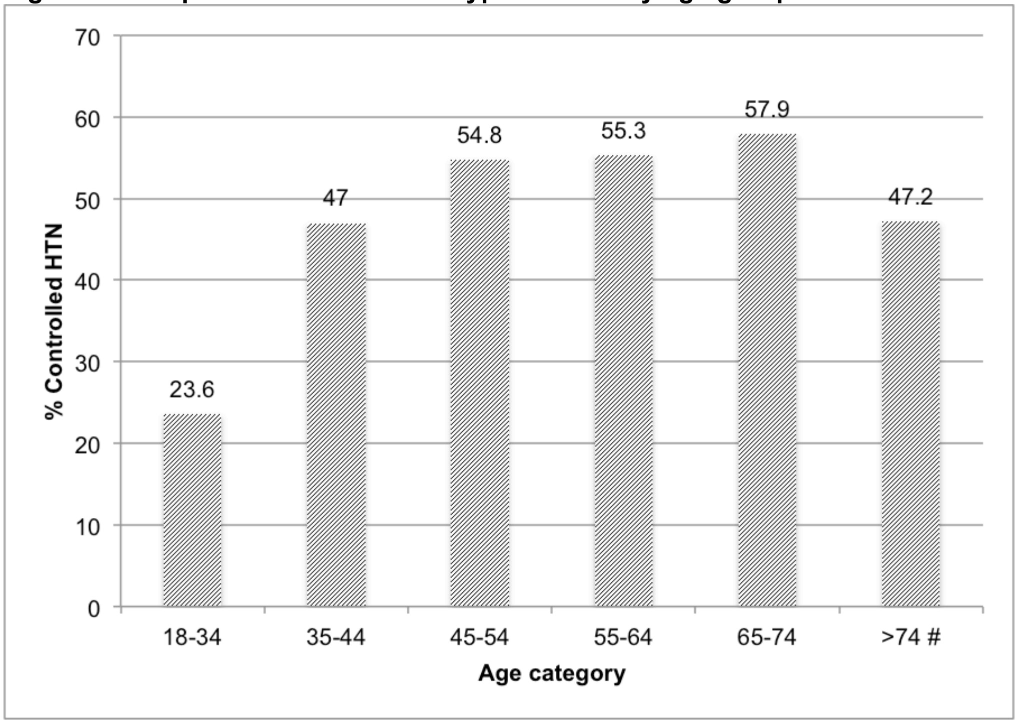
* Traditional USOC includes office, clinic and hospital outpatient department

\# Proportion of population with controlled HYPERTENSION and Emergency Department (ED) USOC significantly different from both no USOC (p=0.002) and Traditional USOC (p<0.001)

\+ No USOC excludes the Emergency Department

Figure 1.2 illustrates the proportion with controlled hypertension by age group. Hypertension control is statistically significantly lower in the youngest (18-34 and 35-44 year olds) and oldest (>74 years old) in pairwise comparisons to each of the three middle age group categories. Only 24% of 18-34 year olds, 47% of 35-44 year olds and 47% of those older than 74 have their blood pressure under control. The proportions with controlled hypertension in the other age groups are 55% (ages 45-54), 55% (ages 55-64) and 58% (ages 65-74).

Figure 1.2 Proportion of controlled hypertension by age group



Proportion of controlled hypertension statistically significantly different between age>74 when compared to age 65-74, age 55-64, age 45-54, and age 18-34 (all p's<0.001). Proportion of controlled hypertension statistically significantly different between age>18-34 and 35-44 when compared to age 65-74, age 55-64, age 45-54 (all p's<0.001). No statistically significant difference in proportion of controlled hypertension between age≥75 and age 35-44 (p=0.27)

Whites are more likely than non-whites to have controlled hypertension (54% vs. 46%, $p<0.01$). Women are more likely than men to have controlled hypertension (55% vs. 48%, $p<0.01$). Those with insurance are also more likely to have controlled hypertension than the uninsured (54% vs. 32%, $p<0.01$). Current smokers are less likely to have controlled hypertension than former smokers and non-smokers (46% vs. 53%, $p<0.01$). Obese individuals are also more likely to have controlled hypertension than those with normal weight (57% vs. 39%, $p<0.05$).

Compared to those older than 35, younger individuals (<35 years old) are statistically significantly *less likely* to have a traditional USOC (72% vs 92%, $p<0.01$) and *more likely* to use the emergency department as their USOC (4% vs 1%, $p<0.01$) or have no USOC (24% vs 6%, $p<0.01$). The youngest are statistically significantly *less likely* to be taking blood pressure medication than older groups (15% vs. 71%, $p<0.01$). The youngest are also *more likely* to have no visits to their providers in the past year (20% vs. 8%, $p<0.01$), meet physical activity guidelines (49% vs. 37%, $p<0.01$) and be current smokers (27% vs. 16%, $p<0.01$) than older groups. In contrast, the oldest individuals (>74 years old) were *more likely* to visit their providers 2 or more times in the past year (91% vs 77%, $p<0.01$) and *more likely* to be taking blood pressure medication (80% vs. 63%, $p<0.01$) than all younger age groups. The oldest (>74 years old) were *less likely* to be smokers (5% vs. 20%, $p<0.01$) and meet physical activity guidelines compared to all other age groups (23% vs. 42%, $p<0.01$).

Multivariable models

Multivariable logistic regression models revealed a significant positive relationship between having a USOC and hypertension control (see Table 1.2). In the full model adjusting for demographics and comorbidities without imputation, those with a USOC had significantly higher odds of hypertension control than those without a USOC [OR=3.89, 95% CI (2.15-6.98)]. The magnitude, direction and significance of the relationship did not change in the imputation model [OR=3.89, 95% CI (2.6-5.83)].

Table 1.2 Odds ratios and 95% confidence intervals for hypertension control

Covariate	Model 1#	Model 2*
Usual Source of Care	3.89 (2.15-6.98)	3.89 (2.60-5.83)
Age strata		
Age >74	0.58 (0.45-0.76)	0.66 (0.53-0.83)
Age 55-64	1.03 (0.79-1.36)	1.01 (0.80-1.28)
Age 45-54	1.1 (0.84-1.45)	1.14 (0.90-1.45)
Age 35-44	0.84 (0.59-1.22)	0.89 (0.65-1.22)
Age 18-34	0.38 (0.25-0.58)	0.42 (0.29-0.61)
Race/Ethnicity		
Hispanic	0.72 (0.56-0.93)	0.72 (0.59-0.87)
Non-Hispanic Black	0.7 (0.59-0.84)	0.75 (0.65-0.87)
Other Race	0.86 (0.60-1.23)	0.81 (0.60-1.11)
Male	0.76 (0.66-0.87)	0.73 (0.65-0.83)
Married	1.22 (1.01-1.47)	1.2 (1.02-1.41)
Insured	1.53 (1.09-2.16)	1.67 (1.3-2.15)
Comorbid conditions		
Heart failure	1.3 (0.94-1.83)	1.28 (0.97-1.69)
Diabetes	1.02 (0.81-1.29)	1.15 (0.94-1.40)
Hyperlipidemia	1.55	1.45

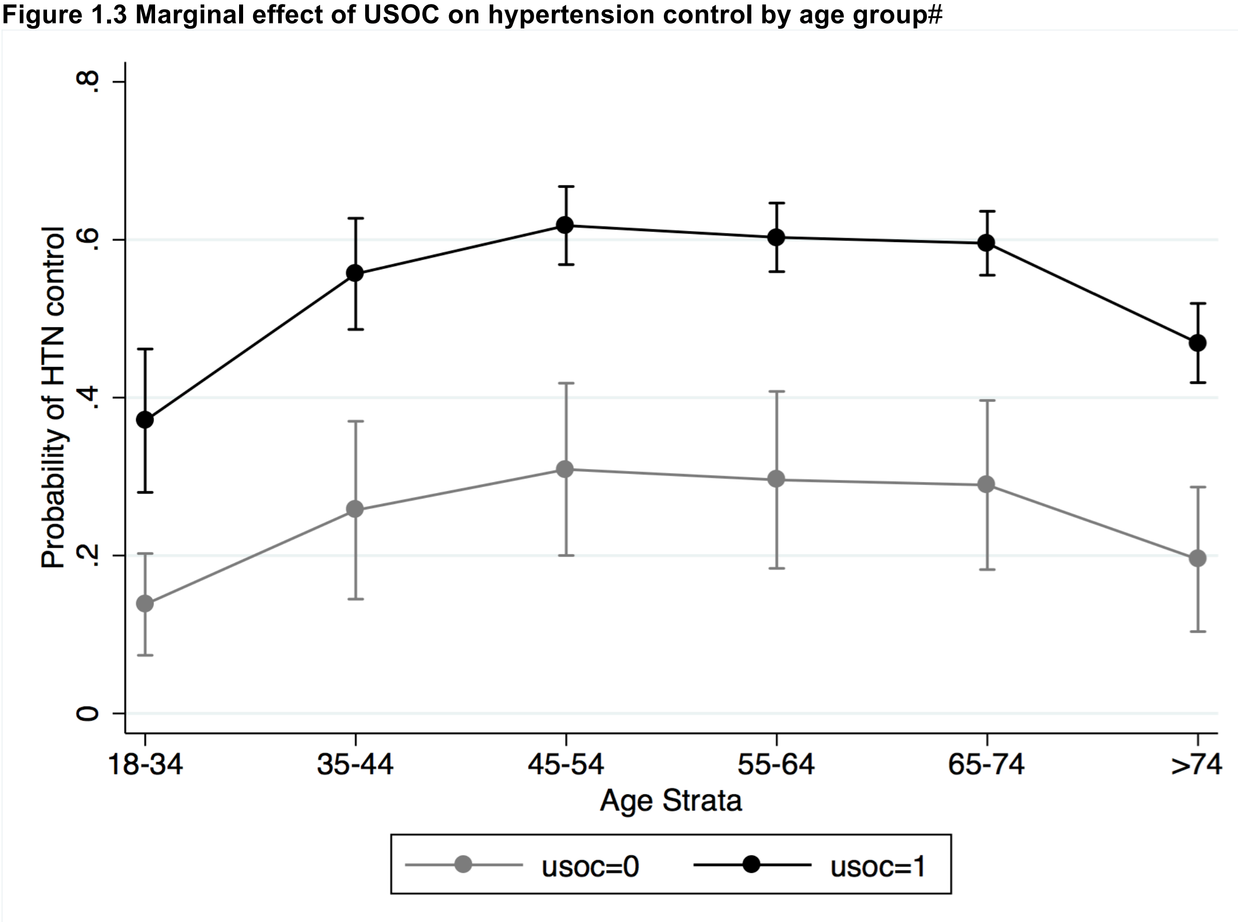
	(1.27-1.90)	(1.22-1.74)
BMI category		
Obese	2.03 (1.58-2.61)	1.94 (1.52-2.49)
Overweight	1.61 (1.23-2.09)	1.62 (1.26-2.10)
Underweight	0.89 (0.28-2.76)	0.87 (0.35-2.17)

#Logistic model controlling for demographics and clinical characteristics
*Logistic model after imputation
Reference categories for multiple category variables are as follows: age 65-74, white race, normal weight. Not all variables in model shown in table.

After controlling for other factors, individuals older than 74 years of age had a 42% lower odds of hypertension control than 65-74 year olds [OR=0.58, 95%CI (0.45-0.76)]. Non-Hispanic Blacks had a 30% lower odds of hypertension control than whites [OR=0.70, 95% CI (0.59-0.84)]; Hispanics had a 28% lower odds of hypertension control than whites [OR=0.72, 95%CI (0.56-0.93)].

In probability terms, the marginal effect of having a USOC is associated with a 30 percentage point higher probability of controlled blood pressure compared to those without a USOC [marginal probability difference=0.30, 95%CI (0.19-0.41)]. This marginal effect amounts to an additional 300,000 individuals with controlled hypertension per million in the US hypertensive population. Figure 1.3 illustrates the marginal effect between USOC and hypertension at each age group. The marginal effect of USOC on the probability of hypertension control in the youngest age group (18-34 year olds) is 0.23 [95 % CI (0.14-0.33)] and in the oldest group (>74 year olds) it is 0.27 [95%CI (0.18-0.36)]. The marginal effect of USOC on hypertension control in 35-44 year olds is 0.30 [95%CI (0.19-0.41)], among 45-54 year olds it is 0.31 [95%CI (0.19-0.43)], among 55-64 year olds it is 0.31 [95%CI (0.19-0.42)], and among 65-74 year olds it is 0.31 [95%CI (0.19-0.42)]. In tests of pairwise comparisons of marginal effects, the 7-8 percentage point difference in marginal effect of USOC on hypertension control in the youngest group (compared to each middle age group) is statistically significantly lower. In terms of the US population this difference amounts to 70,000-80,000 fewer young individuals with controlled hypertension per million individuals with hypertension. The 3-4 percentage point difference in marginal effect in the oldest age group (compared to each middle age group) is statistically significantly lower. This difference amounts to 30,000-40,000 fewer older individuals with controlled hypertension per million in the US hypertension population.

Figure 1.3 Marginal effect of USOC on hypertension control by age group#



The marginal effect of USOC on the probability of hypertension control is statistically significantly lower in the oldest (>74 y.o) and youngest (18-34 y.o.) age groups when compared to all other age groups (p<0.05).

Discussion

In this paper, I discovered several key relationships: (1) a significant positive association between having a USOC and hypertension control in the US population (2) a differential pattern of marginal effects of USOC on hypertension control by age group and (3) different USOC types and behaviors by age group.

The association between USOC and hypertension control captures many pathways through which structural access may impact hypertension control. There are several mediating pathways through which a USOC may operate to improve hypertension control. First, and likely most significant, having a USOC may lead to increased initiation of and adherence to anti-hypertensive medication use given that trust in one's physician has been associated with better medication compliance.[30] Second, patients with a USOC may be more likely to follow up with their providers,[31] allowing for titration of anti-hypertensive medications and discussion of healthy behaviors that lead to improved cardiovascular health. In addition, individuals with other chronic medical issues may be more likely to have a USOC, and management of other comorbidities may increase anti-hypertensive treatment.[32,33]

The reasons for a *changing* relationship between USOC and hypertension control by age group may be the result of differences in health habits, compliance with medication, or dynamic physiologic changes with aging. Some health and nutrition habits that are associated with good overall physical and mental health may been seen in aging, but there are also potential changes in mobility, cognition, and social support– in addition to changes in vascular physiology—that may negatively impact health and blood pressure control.[8,34–36] In our age group analyses older individuals were more likely to follow up with medical providers, be taking blood pressure medication and less likely to smoke. Assuming a mediating role for these factors between USOC and hypertension control, these data suggests that other physiologic factors may be playing a more prominent role in diminished marginal effect of USOC on hypertension control in the oldest individuals. This finding would be in alignment with basic science research demonstrating age-related changes in the blood vessels and chronic physiologic changes in the neural and biochemical systems responsible for regulating blood pressure.[37–42] In contrast, the youngest age groups were more likely to use a different setting for their USOC (i.e., the Emergency Department) that may be less efficient in controlling hypertension long-term. In addition, younger individuals were more likely to be current smokers and have no visits to their USOC in the past year and less likely to be taking blood pressure medication. These findings are in agreement with another study showing that infrequent healthcare may be a significant contributor to undiagnosed and/or untreated hypertension in the youngest individuals.[43] Thus, in younger individuals behavioral factors may play more of a role in the diminished marginal effect of USOC on hypertension control.

There are several limitations to this study given the cross-sectional design, measurement of hypertension, potential endogeneity of USOC and subpopulation sizes. With a cross-sectional design the causality underlying the observed relationship between USOC and hypertension control cannot be determined. Although blood pressure was measured by trained professionals, hypertension status and control are based on the average of two readings in a single evaluation. If there was “white coat” hypertension that varied by USOC status, we may have overestimated or underestimated the effect of USOC on hypertension control. Moreover, if such white coat hypertension varied by age groups, that may have altered the differential marginal effect of USOC on hypertension control across the age groups. In terms of endogeneity, it is possible that those with controlled hypertension may be more likely to report a USOC or have other unmeasured factors that would change the association between USOC and hypertension control in the US population. Finally, given the low sample size in the oldest age group without a USOC, statistical power is limited to obtain precise estimates.

Despite these limitations, the study remains robust given the control for major confounders and an imputation analysis that gives a range of potential effect of USOC on hypertension control. In addition, the relationship between USOC and hypertension—and the differential effect of USOC on hypertension across age groups—was consistent across the imputed and non-imputed multivariable models. Finally, this is a nationally representative sample that has high external validity.

Conclusion

This study supports the positive effect of USOC on hypertension control in the US population and the changing dynamic of a USOC on hypertension control across the age spectrum. The morbidity, mortality and costs from hypertension in the general US population are enormous, with poor outcomes as people age. Thus, discovering the beneficial role that having a USOC plays in hypertension control across the entire population is key to assist with policy decisions to improve access to regular sources of care. In addition, the varying impact of USOC on hypertension control across age groups may reflect a need to change strategies to control blood pressure in different age groups. Specifically, a focus on improving health behaviors in younger individuals may involve focusing on anti-hypertensive medication initiation and compliance, regular follow up, and cessation of smoking. Conversely, given that the effect of having a USOC on blood pressure control is diminished in the oldest population, more information is needed to discover what strategies will most effectively improve health outcomes in the oldest and most vulnerable. Given shifting guidelines and newer data from the Systolic Blood Pressure Intervention Trial (SPRINT) suggesting lower blood pressure targets have improved cardiovascular morbidity and mortality outcomes in higher risk patients,[44] it will be important to continue to monitor hypertension control and the cardiovascular sequelae in those most susceptible to poor outcomes.

Chapter 2

Age Group Differences in Emotional Health Among Heart Failure Patients

This chapter will explore the following two questions:

Question 2a: Does emotional health in patients with heart failure vary by age?

Question 2b: Do social isolation and/or physical health mediate the association between age and emotional health in patients with heart failure?

Background

Heart failure is the number one cause of hospitalization in the Medicare population, and places a heavy economic burden on the health care system.[1,45] Estimated total costs were $30 billion in 2012, accounting for 1-2% of health care expenditures. Additionally, the projected total costs due to heart failure are expected to increase to $77 billion by 2030.[1]

Incidence of heart failure after the age of 65 is approximately 10 per 1000, increasing to 40 per 1000 in those over 85 years old. And, the U.S. population is aging. Currently, over 40 million people in the U.S. are 65 years of age or older, with rate of growth in that segment exceeding the rate for the total population.[46] The number of people older than 85 years old is expected to rise significantly, from 5.8 million in 2010 to 19 million in 2050.[47]

Defining and Measuring HRQOL in heart failure

Documenting the impact of heart failure on health-related quality of life (HRQOL) relies on precise definitions and quantitative measurements. Over 50 years ago, the World Health Organization defined health as a total state of mental, physical and social well-being.[48] Echoing the WHO definition of health, HRQOL is a *multidimensional* concept, encompassing one's ability to engage in daily functions and one's feelings of well-being.[49–51]

HRQOL is assessed using generic instruments (e.g., the Short Form-36 or SF-36) or disease-targeted instruments (e.g., the Minnesota Living with Heart Failure Questionnaire (MLHFQ) or Kansas City Cardiomyopathy Questionnaire (KCCQ)). The SF-36 yields 8 mutli-item scales (physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional and mental health) and 2 summary measures (physical health and mental health).[52,53] Generic measures allow the comparison of HRQOL across multiple disease states and have been in wide use for over 30 years.[54–56] However, more specific effects of heart failure may be better assessed by targeted instruments.

The MLHFQ and the KCCQ, the two most widely-used HRQOL instruments for heart failure, contain questions targeted at heart failure's multidimensional impact.[57] The KCCQ contains 23 items covering 6 domains (physical limitation, symptoms, symptom stability, self-efficacy, QOL, and social limitation); the MLHFQ contains 21 items covering two main domains (physical health and emotional health), in addition to an "other" domain that encompasses socioeconomic stress (e.g., medical costs) and side effects of treatments.[58–60] Disease-targeted instruments may more accurately reflect severity of heart failure and be more responsive to change from clinical interventions.[57,61–64] The MLHFQ has been evaluated in multiple settings with wide variations in demographic characteristics and correlates highly with measures of depression as well as other generic HRQOL measures like the Short Form-12 (see Table 2.1).[59–61]

Table 2.1 Minnesota Living with Heart Failure questionnaire correlation with other measures*

Measure	Correlation with MLHFQ summary score
Beck Depression Inventory	0.62
Brief Symptom Inventory—depression subscale	0.64
SF-12 overall score	0.61
SF-12 mental subscore	0.68
SF-12 physical subscore	0.57
Chronic Heart Failure (CHQ) total score	0.81
CHQ Emotional score	0.74

*Table adapted from Rector, T.S. Overview of the Minnesota Living with Heart Failure Questionnaire. 2005. Accessed at: http://license.umn.edu/technologies/94019_minnesota-living-with-heart-failure-questionnaire

Heart failure's impact on HRQOL

Heart failure negatively impacts HRQOL, potentially through multiple mechanisms, including repeated hospitalizations, polypharmacy and medication side effects.[54,65–69] Heart failure patients' HRQOL scores are substantially below those of the general population with gaps similar to those seen in other severe chronic comorbidities.[6,54,70,71]

Focusing in on the emotional health HRQOL subcomponent is critical for understanding the impact of cardiovascular disease in general, and heart failure in particular. Emotional health (as defined for this dissertation) is the dimension of the MLHFQ that concerns how one's heart failure causes depression and worry, affects concentration and self-control, and increases a patient's sense of being a burden for family and friends.[59]

Emotional health predicts incident cardiovascular disease as well as hospitalization, mortality and progression of heart failure.[72–75] In addition, monitoring and evaluating emotional health may improve communication between physicians and patients and provide targets for therapeutic intervention.[76–80] Depressive symptoms (components of emotional health usually defined by a questionnaire) are highly prevalent in heart failure, impacting between 30-50% of patients.[54,81–85] Major Depressive Disorder (as defined by the Diagnostic and Statistical Manual of Mental Disorders-IV) is less prevalent (around 20%) than depressive symptoms but is found at levels almost 4-5 times higher in persons with heart failure than in the general population. [56,86–89]

Emotional health is an important dimension in heart failure that may serve as a better indicator than other generic measures for detecting important changes in heart failure patients' mental health.[90] Nevertheless, despite the indisputable significance of emotional health, very few studies have looked specifically at the emotional health dimension in the Minnesota Living with Heart Failure Questionnaire (MLHFQ). Previous studies have evaluated specific components within the MLHFQ (like sexual functioning),[91] but more research is necessary that focuses on the domain of emotional health more broadly.[92]

HRQOL in Heart Failure Patients Across the Age Spectrum

As patients with heart failure age, some researchers have hypothesized that increasing comorbidities negatively impact HRQOL compared to younger heart failure patients; however, others note that adjustment to physical limitations, changes in expectations, or improved spiritual well-being in older patients may improve HRQOL in heart failure.[6,54,65,66,84] In one study of 400 patients with heart failure, those ≥65 years old had better baseline HRQOL scores than those <65, but older patients' scores declined more significantly over a one-month period.[65] In another study of 160 patients, older subjects reported significantly *worse* physical functioning (on the SF-36 physical functioning subscale) but there were no significant differences in the SF-36 overall score.[66] In a smaller and younger cohort of heart failure patients (mean age 46), "older" patients (age cutoff or age range not listed) reported more vitality on the SF-36, but the total score on the instrument was not different.[84] A larger study that stratified by age groups found that younger patients reported worse HRQOL as measured by the MLHFQ in bivariate analyses, likely as a result of higher symptoms of depression and anxiety in the youngest strata.[93] In a large clinical trial of 800 patients with NYHA class III-IV on optimal medical therapy, there were no age differences in HRQOL, but approximately 50% of that population did report symptoms of depression and anxiety. In another small heart failure study, there were no age differences in total SF-36 scores, but older age was associated with lower scores on the SF-36 role-emotional subscale.[54] And in one study of 100 outpatients with heart failure at a tertiary care referral center, emotional health was better in younger patients than in older patients (as measured by the mental health score on the SF-12); changes in age accounted for approximately 9% of the variability in emotional health.[92] Thus, the literature is mixed on age-related differences in HRQOL and speaks to the need for greater clarity in HRQOL outcomes in the heart failure population.

The role of social isolation

Social isolation can be defined as the lack of social support (emotional, social or physical) from family and friend networks.[94] Multiple small studies have evaluated the potential role of social support in HRQOL in heart failure patients.[95–99] Each study demonstrated that better social support is associated with lower levels of depressive symptoms, resulting in better HRQOL.[95,98] With respect to aging, there appear to be complex changes in social support networks; overall support networks tend to decline, but family support may remain more stable over time.[100–102] The differing mental and physical experience of heart failure in older patients in some studies may be affected by patients' changing expectations about functional limitations or differences in social support.[93,95,98,103] Thus, this project aims to clarify the level of social isolation in a large heart failure population and whether isolation impacts emotional health differentially across the aging spectrum.

The role of physical health

Physical health and emotional health are complex components of HRQOL and may have bidirectional effects on each other in chronic disease.[56,72,104–106] Among patients with chronic illness (including patients with cardiovascular disease), physical health had positive causal effects on downstream emotional health.[105] In a small heart failure cohort, both physical symptom status (as defined by the Dyspnea and Fatigue Index(DFI)) [107] and anxiety (as measured by the Brief Symptom Inventory)[108] were the main components causing variation in MLHFQ scores.[70] In another study of heart failure patients recently discharged from the hospital, baseline physical symptom status, again measured by the DFI,[107] was associated with downstream MLHFQ scores (with increased physical symptoms associated with poorer HRQOL).[109] The circular nature of these associations are important to note, however, as they each use measures of physical symptoms (i.e., DFI) which are similar components within the MLHFQ measure itself. Thus, rather than looking at how physical symptoms are associated with HRQOL measures (like the MLHFQ), it may be more prudent to evaluate physical health and emotional health separately in heart failure patients and how the two are inter-related. Moreover, the role that physical health may play in *mediating* the association between age and emotional health in heart failure patients is unknown. This study aims to address these lacunae.

Study aims

Important associations have been demonstrated along the individual pathways related to the relationships between aging, social support, physical health and emotional health, but more research is required to elucidate these complex relationships in a large and diverse population of heart failure patients. Thus, this study will advance the literature by: (1) providing additional data about the differences in emotional health across age groups in heart failure patients using a large sample of heart failure patients from a clinical trial, and (2) analyzing social isolation and physical health as potential mediators between age and emotional health in this large cohort of heart failure patients.

Conceptual Model

The primary relationship being assessed is the association between age and emotional health, defined by emotional dimension scores on the MLHFQ (see Figure 2.1, arrow 2a). The additional relationships of interest in question 2b (Figure 2.1, arrows 2b) are the mediation effects of social isolation and/or physical health between age and emotional health.

Figure 2.1 Conceptual model for age and emotional health

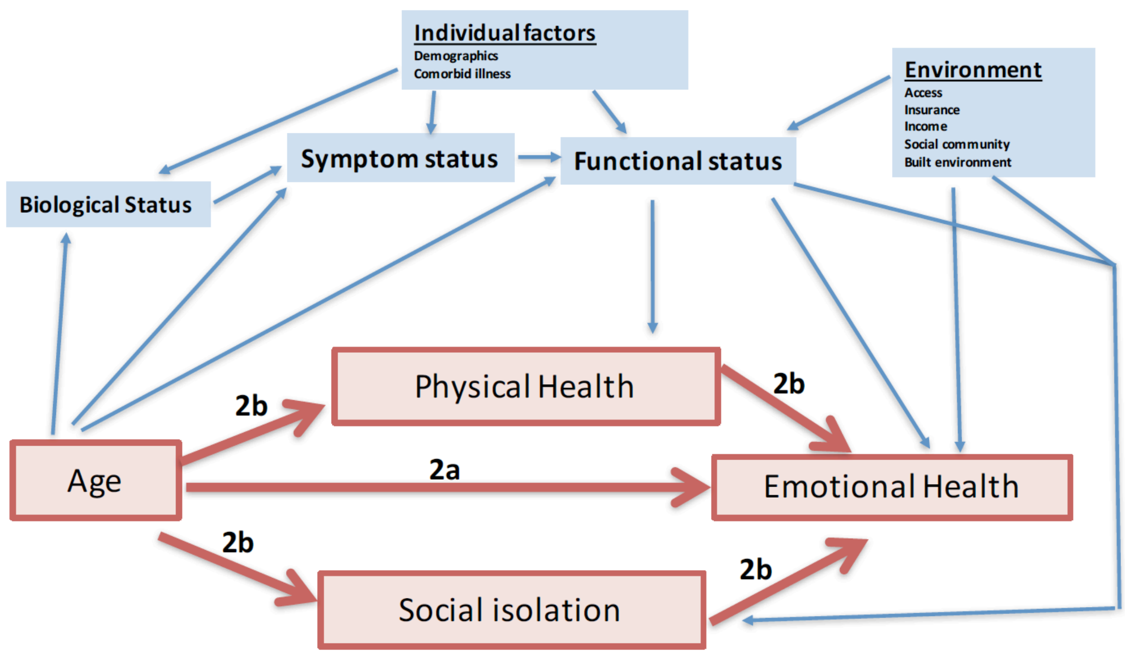


Figure 2.1 Legend:
Red boxes—primary measured variables of interest
Red arrows—primary relationships tested in statistical models
Blue boxes—other measured and unmeasured concepts and variables
Blue arrows—relationships between concepts/variables that indicate main causal direction (some level of bidirectionality assumed)

The conceptual model is adapted from the framework initially set out by Wilson and Cleary[110], and subsequently modified by Ferrans and colleagues to incorporate individual and environmental factors.[111,112] Wilson and Cleary initially set out to describe several domains that impact the end-result of health-related quality of life: (1) biologic factors, (2) symptoms and (3) functional Status. Biologic factors encompass those elements that are measured by lab tests (i.e. Creatinine, BNP) or on physical assessment (i.e., murmurs, rales) that can be utilized to make diagnoses. Biology/physiology, in turn, impacts symptom status (e.g., shortness of breath) which impacts functional status. Ferrans and colleagues augment the functional status component of the model to encapsulate functional capacity (maximal ability to perform a given emotional or physical task), performance (day-to-day activity), utilization (percentage of functional capacity), and reserve (or "unused" potential).[111] All of the prior components (biology, symptoms, and functional status) then influence health perceptions, or the individual subjective rating of one's health status (emotional and physical health). In this model, the terminal component (or outcome) is the rating of how one's heart failure impacts their emotional health.

Ferrans' model adds to the Wilson and Cleary model by highlighting two main external components that impact biology, symptoms, functional status and health perceptions: (1) *Individual factors* (e.g., gender, race/ethnicity, education, and comorbid illness) and (2) *Environmental factors* (e.g., income, insurance, access to health clinics, social community and the built environment). Two simple examples may help illustrate the role of individual and environmental factors in the pathways illustrated. First, individual factors such as education or health literacy may impact knowledge about one's illness, perceptions of illness or even self-determination to carry out a functional task.[113,114] On the environmental level, one's social community, income, or insurance status impact how, when, and where treatment is sought (or adhered to) which then can impact how one rates the impact of illness on their emotional or physical health.[110–112]

In the conceptual model, I note two factors—social isolation and physical health—which may mediate the relationship between age and emotional health. Greater comorbid illness burden in heart failure patients may be associated with greater severity of symptoms, decreased ability for self-care, higher levels of polypharmacy, and increased prevalence of medication side-effects that may impact one's rating of physical health, which may then impact how they perceive their illness impacting emotional health. Comorbid burden may also impact emotional health through limitations in functional capacity, functional performance, and functional reserve which may lead to depression and social isolation. Turning specifically to social isolation, as one ages isolation may increase through both physical limitations and death of friends and family members. Social isolation can have several ramifications: inability to manage one's own illness(es) and lack of emotional interaction with people within the healthcare system (i.e. providers) as well as friends and family. Thus, social isolation can clearly impact emotional health.

Methods and Measures

Data Source

The Better Effectiveness After Transition-Heart Failure (BEAT-HF) study is a multicenter trial comparing the impact of wireless remote monitoring and nurse coaching to usual care for heart failure patients discharged to home after an index hospitalization for decompensated heart failure. Patients in the intervention arm received several types of telephone contact with nurses: (1) structured telephone phone calls from a centralized call center nurse (at least once a week for the first month post-discharge and monthly for the remainder of the six month study period), and (2) potential additional calls based on upon the information gathered during the scheduled call center phone calls or their health based on daily wirelessly transmitted data (answers to general health and heart failure-related questions in addition to weight, heart rate, and blood pressure)[i]. Patients 50 years of age and older were included if they were hospitalized with heart failure at any of six California medical center study sites (UCLA, Cedars-Sinai, UCSF, UCD, UCI, and UCSD). The primary exclusions were patients who were in skilled nursing facilities, those with dementia, those on chronic dialysis, and patients without a working telephone. After assessment for eligibility, 1437 patients were included in the study. The primary outcome of the trial is the 180-day re-hospitalization rate. Secondary outcome measures are mortality rates and the MLHFQ health-related quality of life score. The primary outcome papers, comparing the effects of the intervention on these measures, have already been published.[115,116]

Patients in the trial were administered a baseline MLHFQ questionnaire via face-to-face interview by trial study staff during their initial hospitalization before randomization.[116] The MLHFQ contains 21 items, 8 specifically focusing on physical health and 5 on emotional health. Items are scored on a 6-point 0-5 categorical response scale. The 21-item total score ranges from 0-105; the physical health score from 0-40, and the emotional health score from 0-25. *Lower* scores indicate *better*

[i] Six questions were transmitted by the equipment to the patient. Answers were transmitted back to a centralized call center. Each day patients received 3 of the six questions. Set 1: (1) Compared to yesterday, would you say you are feeling about the same, better, worse, or much worse? (2) Did you wake up more short of breath last night? (3) Did you sleep in a chair, or propped up on pillows, more than usual last night? or Set 2: (1) Have you felt more short of breath in the last day? (2) Have you noticed more swelling in the last day? (3) Have you had any light-headedness or dizziness in the last day?

health. Cronbach's alphas of ≥0.9 for the overall measure, ≥0.85 for the emotional health scale, and ≥0.90 for the physical health scale have been reported.[59,117,118]

Measure definition and construction

See Table 2.2 for the list of concepts, variables, and construction. The table contains additional information on justification and limitations.

Table 2.2 Concepts and Measures

Concept	Variable	Variable construction	Justification	Limitations
Main Outcome				
Emotional Health	Emotional Health (EH) score	Continuous variable based on answer to 5 questions on the emotional dimension sub-section of the MLHFQ. Also constructed into quartiles. Higher scores indicate WORSE EH.	EH is a critical component of HRQOL and patient reported outcomes are becoming increasingly important in the management of chronic diseases such as heart failure.	5 questions will not fully encompass all aspects of heart failure-related EH.
Primary predictor				
Multidimensional: coping skills, time-related physical changes, frailty	Age	Dummy encoded for three age strata: Age 50-64, 65-79, and >79. Reference category will be 50-64 age group.	Constructing age in broader categories allows assessment of wider trends in age-related perceptions of illness and EH. Age may also modify the association between other variables (social isolation) and EH.	Loss of variability in using age-strata. May miss finer associations between changes in age and EH.
Mediating variables				
Physical Health	Physical health score	Continuous variable as defined by score on 8 questions in MLHFQ that relate to physical health in factor analysis	Physical health changes over time (with age) and may also impact emotional health (i.e. more physical limitations may generally lead to worse emotional health).	8 items only related to heart failure impact on physical health. There may be other non heart failure related physical limitations that impact emotional health. Also EH may be a driver of physical health (possible reverse causality).

Social isolation	Social network scale	Continuous variable as defined by score on the Lubben Social Network Scale-6 (scored 0-30 overall based on 6 items about family and friends). Will also use dichotomous <=12-point cutoff that has been used in the literature to define "isolation"	Social isolation is a key theoretical driver of EH. Social isolation may be a mediator between age and EH.	Using a cutoff point may miss finer associations with EH. Shorter 6 item questionnaire does not encapsulate all aspects of social isolation.
Other covariates				
Access to services	Insurance	Insured=1, uninsured=0	Insurance allows for "potential" access which may enable better heart failure care and improve EH.	Potential access may not be realized access The measure construction may miss finer associations between types of insurance and EH
	Household income	Four dummy encoded categories (1/0): Household income <25K, 25-50K, 50-75K, >75K.	Income measured at a household level encapsulates varying degrees of family poverty and may effect adherence to medications, stress, anxiety and EH.	Household income does not capture overall family wealth. The measure construction may miss finer associations between income and emotional EH.
Intrinsic factors	Gender	Dichotomous: Male=1, Female=0	Gender impacts perceptions of illness, may impact coping and EH.	Gender a complex construct, but no major limitations.
	Education	Three dummy encoded categories: Less that high school, high school grad, and college grad	Education impacts knowledge of illness and perceptions of heart failure	The construction of education may miss finer associations between varying levels of higher education.
	Race/ethnicity	All dummy encoded (1/0): Hispanic, Non Hispanic White, Non Hispanic Black, Other Race. Non Hispanic White is reference group.	Race/ethnicity captures cultural differences in health beliefs and care-experiences.	Within racial and ethnic categories likely a lot of heterogeneity in health behaviors, coping skills. Also cannot assess categories within "other race".
	Health Literacy	Score on REALM-D: Dichotomous variable based on score <6 indicating "at risk for health literacy issues"	May impact knowledge of illness and perceptions of heart failure	Literacy and education may encompass similar concepts. Dichotomous variable loses variability.
Comorbid illness/Severity of other illnesses	Comorbidity variables: MI (prior heart attack), CVA (stroke), DM (diabetes), COPD (Chronic obstructive lung disease), ESRD	Dichotomous variables (other than creatinine) based on ICD-9 codes on admission.	Presence and number of comorbidities captures health status broadly and impacts EH	Presence of comorbidities does not measure functional status (e.g. how severe one's valvular disease is or how it impacts their functional capacity).

The following is the list of variables and their construction:

Outcome variable

Five questions on the MLHFQ represent emotional health:

*Did your **heart failure** prevent you from living as you wanted during the past month by making: (1) you feel you are a burden to your family or friends? (2) you feel a loss of self-control in your life? (3) you worry? (4) it difficult for you to concentrate or remember things? and (5) you feel depressed?*

Patients answer each question from 0-5, where 0 means “no,” 1 means “very little,” and 5 means “very much” (2, 3 and 4 are not labeled). Scores of emotional health range from 0-25. The patient’s baseline emotional health is treated as continuous; in addition, the score is divided into quartiles for further analysis. Higher scores indicate worse emotional health.

Primary predictor

- Age is discretized into three groups: 50-64 years old, 65-79 years old and >79 years old.

Control variables

- Health literacy is assessed using the Rapid Estimate of Adult Literacy in Medicine, Revised (REALM-R). A dichotomous variable is created where a score of 6 or less is “At risk for poor health literacy.”

- Education is in three categories: less than high school, high school graduate, and college graduate.
- Race/ethnicity is categorized as Non-Hispanic Black, Non-Hispanic White, Hispanic and other race.
- Gender is categorized as male or female.
- Annual family income is divided into 4 categories: <$25,000, $25-50,000, $50-75,000, and >$75,000.
- The presence of certain comorbidities (i.e. COPD, DM, MI, atrial fibrillation) are dichotomous variables based on admission ICD-9 codes.

Potential mediating variables

- Social isolation is assessed using the Lubben Social Network Scale-6 (LSNS-6).[119,120] In an elderly cohort of patients, LSNS correlated with hospital use, life satisfaction and health behaviors (i.e., lower scores were associated with more hospital use and less satisfaction).[121] A social isolation "cutoff" of 12-points or below is used to define those as isolated, as has been done in prior studies.[120,122]
- Physical health is represented by the 8-items physical health scale score on the MLHFQ. Scores are continuous and range from 0-40. *Lower* scores indicate *better* physical health.

Construct validity variables

- The Geriatric Depression Score (GDS) gauges the presence and level of depression. Scores of 0-4 are normal, 5-8 are suggestive of "mild depressive symptoms," 9-11 is suggestive of "moderate depressive symptoms," and 12-15 indicates "severe depressive symptoms."[123] These four mutually exclusive categories will be created and used in addition to the continuous score in separate analyses.

- New York Heart Association Class (I-IV) is the clinician assessment of heart failure's impact on the patient's physical health. NYHA class is reported on initial nursing screening and is a categorical variable.

Statistical methods

Univariate analysis

For continuous variables I report their mean, standard error and display a histogram. For categorical variables, I report the proportions in each category. I also assess the percentage missing for each variable.

Analysis of questionnaire

Reliabilities of the MLWHFQ 21-item total score, 8-item physical health scale, and 5-item emotional health scale are estimated using Cronbach's alpha.[124] Multi-trait scaling is utilized to assess the extent to which items are correlated more strongly with the scale they are hypothesized to assess (corrected for item overlap with the total score) than with other scales.[125] Construct validity of the emotional health dimension is assessed by correlations with the Geriatric Depression Scale. Scatterplots are analyzed to assess the linearity of the relationship between Geriatric Depression Scale (GDS) and the emotional health score. Given that the relationship appears linear Pearson's correlation coefficient may be the better test for assessing construct validity. I calculate Pearson's correlation coefficient (r) and r^2 to determine the proportion of shared variance between the two variables. However, I was also interested in the mean emotional health scores in the extreme depression group compared to all others. Therefore, in addition to Pearson's *r* I report effect size (Cohen's d) to assess the difference in mean emotional health scores between those with major depressive symptoms (GDS≥12) and the rest of the heart failure population (GDS≤11).[126] Bootstrapped 95% confidence intervals for the effect sizes are calculated given the potential for non-central t-distribution.[127] I hypothesize that the product-moment correlation and effect sizes will be "large" (r=0.371 or larger; d=0.8; or 0.8 standard deviation difference between the mean emotional health scores) given the degree of overlap between the GDS and emotional health subscale scores.

Bivariate analysis

Because of a clinical interest in analyzing relationships between covariates and those with the worst emotional health, patients are separated into two groups (the worst quartile of emotional health vs. all others). I assess relationships between covariates and emotional dimension quartile with the χ^2 test for categorical variables and the t-test for continuous variables.

Because of conceptual overlap between education and health literacy, collinearity between the two variables is evaluated using the variance inflation factor (VIF); if VIF>2.5 only one of the variables is used in the regression models (see below).

Missing data imputation methods

I utilize multiple imputation using the chained equations method, given its validity in dealing with both categorical and continuous variables.[26] This method uses separate regression models for each variable: linear regression (or truncated linear regression) for continuous variables, logistic regression for dichotomous variables, and multinomial or ordinal logistic regression for categorical variables. The other variables in the imputation model are used as predictors; once a value is imputed for a missing variable it is then used to impute the next missing variable, but the order of imputation begins with the most observed (i.e., least missing).[27,28] I create five multiply imputed datasets (M=5) as is recommended in the literature.[27] Results are then aggregated across the imputed data sets to properly account for between imputation variance. Imputation analyses are utilized as secondary sensitivity analyses.

Regression analyses

Research question 2a: Do emotional scores vary by age group?

Given the continuous nature of the emotional health outcome variable, the primary model for answering this question is a multivariate linear regression (OLS model), controlling for age group and other control variables listed above in the measure definition section. One of the main assumptions of OLS is that the errors have uniform variance (i.e., homoscedastic), thus, I test for this assumption using the Cook and Weisberg test. To reduce inefficiency in the models collinearity between variables is assessed using the variance inflation factor (VIF); if VIF>2.5 the variable is removed and VIF reassessed (with a goal mean VIF approximately 1). Given the heteroskedascticity in the data, I also employ regression with robust standard errors (Huber-White sandwich method), robust linear regression with iterative weights, and robust regression controlling for clustering by hospital site. These methods allow for better estimation of standard errors (in the case of the Huber-White sandwich method) and coefficients (in the two robust regression methods) if there are minor violations of the assumptions of OLS. However, each of these methods yield similar results and the primary model for assessing the association between age and emotional health is the standard OLS multivariable linear regression model given the consistency and efficiency of estimates. Other models described below are additional sensitivity analyses.

Given the relatively equal distribution of the emotional health subscale scores (based on univariate analyses) across quartiles and clinical interest in the factors affecting the emotional health outcome at the extremes, I pursued quantile regression to allow for the effect of age (and other covariates) to differ across the range of emotional health scores. Quantile regression allows testing of this variation and is a preferred over a stratified ordinary least squares (OLS) model because it utilizes the entire sample. [128] I use quantile regression to evaluate the association between the independent variable of interest (age) and quantiles of the outcome (emotional health). I run quantile regression simultaneously (using the sqreg function in STATA) and test for equality of coefficients across quantiles. A graph representing the effect of age on emotional health in each quantile is presented to visualize the potential changing association across the range of scores.

The above models analyze baseline emotional health in the BEAT-HF trial. There is additional longitudinal data on emotional health. Thus, I also fit a model that accounts for the longitudinal nature of the data and utilizes emotional health scores from all time-points in the BEAT-HF trial (baseline, 7, 30 and 180 days). While mixed effects linear regression is a generally sound model dealing with longitudinal data (yielding consistent and efficient parameter estimates for variables as long as observations are missing at random) there is approximately 50% of the outcome questionnaire data missing at 180 which is of concern. Thus, this method is not preferred over standard multivariate linear regression using baseline data alone. A mixed effects linear regression model takes into account the correlation of the outcome over time within patients and controls for the covariates using fixed effects and random effects. I utilize multivariable models incorporating patient-level random effects (random intercepts and random slopes for emotional health outcome) as well as hospital site random effects (random intercepts and random slopes). In random slope models, I alter the covariance structure to unstructured and exchangeable and assess model fit over a random-intercept only model using the LR test.[ii]

Research question 2b: Are physical health and social isolation mediators of the association between age and emotional dimension scores?

The primary analysis utilized to test mediators between age and emotional dimension scores at baseline estimates simultaneous multivariable regression models and allows the error terms to be correlated (i.e., “seemingly unrelated regression”). The analysis uses complete cases. This method was chosen as the preferred method to allow estimation of the proportion of mediation, maintain the age variable as categorical as in the primary regression analyses, and controls for additional covariates. Direct and indirect effects are estimated by product coefficients: nonlinear combination of coefficients (for indirect pathways a1*b and a2*b) and linear combinations of coefficients

---

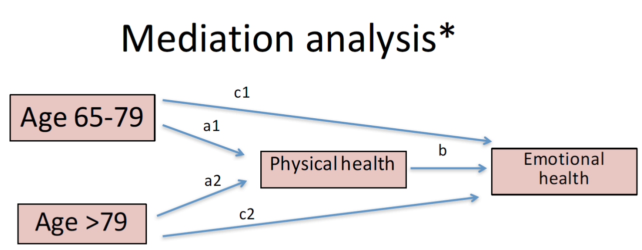
[ii] Unstructured covariance matrix estimates all variances and covariances. $Var_i(\theta) = \begin{bmatrix} \sigma^2{}_1 & \sigma_{12} & \sigma_{13} & \sigma_{14} \\ \sigma_{12} & \sigma^2{}_2 & \sigma_{23} & \sigma_{24} \\ \sigma_{13} & \sigma_{23} & \sigma^2{}_3 & \sigma_{34} \\ \sigma_{14} & \sigma_{24} & \sigma_{34} & \sigma^2{}_4 \end{bmatrix}$

The exchangeable covariance matrix assumes all variances are equal to one and all covariances are equal. $\boldsymbol{R}_i = \sigma^2 \begin{bmatrix} 1 & \rho & \cdots & \rho \\ \rho & 1 & & \rho \\ \vdots & & \ddots & \vdots \\ \rho & \rho & \cdots & 1 \end{bmatrix}$

(for direct pathways c1 and c2).[iii] The nonlinear combination of coefficients ("nlcom") uses a method to calculate standard errors that assumes a normal distribution which may be incorrect. Thus, bias-corrected bootstrapped 95% confidence intervals are utilized for the indirect effects to determine statistical significance of each pathway.[130] Social isolation was not found to be independently associated with emotional health scores in the multivariable model so it was not included in this mediation analysis, but was included as a covariate in the simultaneous multivariate regression models.

Figure 2.2 shows the mediation model for the relationship between age group, physical health and emotional health.

Figure 2.2



*Seemingly unrelated regression uses simultaneous regression equations and allows error terms to be correlated. The model controls for variables significant at p<0.20. Reference category for age is 50-64 year olds.

In addition to the mediation method above, I perform sensitivity analyses using structural equation modeling which allows joint fitting of complex relationships.[131,132]

[iii] The mediation analysis is conducted in STATA as follows:

sureg (*mediating_var i.categorical_independentvar*)(*dependent_var mediating_var i.categorical_independentvar*)

In the model with additional control for covariates in each part it becomes:

sureg(*physical i.age_category $covariates*)(*emotional physical i.age_category $covariates*).

Generalized structural equation modeling (gsem) allows utilization of categorical variables and handles the use of multiple models (e.g., logistic model to assess association between physical health and the dichotomous social isolation variable, and linear regression to assess association between age strata and emotional health). I also employ two different types of structural equation modeling both of which require age and social isolation to be continuous variables: path regression (pathreg in STATA) and structural equation modeling (sem in STATA) accounting for clustering by site location[iv]. Sobel-Goodman mediation tests are used to estimate the proportion of the total effect of age on emotional health that is mediated by physical health using all as continuous variables.[133]

Sensitivity analysis

The “gold standard” model for question 2a is linear regression given efficiency and consistency of the model estimates. Additional models will explore the potential range of effect of age on emotional health scores:

(1) A limited regression model that includes only variables with minimal missing values (less than 3%)

(2) A limited regression model including variables whose coefficients in the complete-case multivariable model that have a p-value<0.20.

[iv] gsem in STATA allows for dichotomous variables and various modeling based on the nature of the outcome variable (logistic, linear, etc.). pathreg and sem in STATA require variables to be continuous; sem gives an additional advantage of being able to control for clustering by hospital site.

Results

Univariate

See Table 2.3 (below) and Figure 2.3 (in the Appendix) for univariate analyses in the BEAT-HF population. The study had 1437 patients at baseline. Thirty-six percent of the patients in the trial were 80 years of age or older, 45% were female, and 55% were Non-Hispanic white. Thirty percent of the population was at-risk for poor health literacy (i.e., REALM-R scores < 7), while 15% had less than a high school education.

Table 2.3 Univariate statistics for the BEAT-HF population

Variable	Number (or mean)	Percent (orSD)
Age strata		
50-64	417	29.00%
65-79	507	35.30%
>79	513	35.70%
Gender		
Female	664	46.20%
Race/ethnicity		
Hispanic	163	11.40%
Non-Hispanic Black	316	22.10%
Non-Hispanic White	779	54.50%
Other race	171	12%
Marital status		
Married	585	41.90%
Divorced	318	22.80%
Widowed	332	23.80%
Never married	160	11.50%
Education		
Less than high school	212	15.20%
High school graduate	728	52.30%
College graduate	453	32.50%
Health literacy		
At risk for poor health literacy	428	30.30%
Annual household family income		
<$25 K	443	40.00%
$25-50K	285	25.70%
$50-75K	163	14.70%
>$75K	218	19.70%
Social isolation		
Lubben social network Scale score (mean, SD)	17.2	6.7
"Isolated" (LSNS<12)	292	21.30%
Minnesota Living with Heart Failure Questionnaire		
Total score (0-105)	60.4	26
Physical health score (0-40)	31.5	11.7
Emotional health score (0-25)	12.2	7.6
Social/other health score (0-40)	16.8	9.5
NHYA class		
Class I-II	294	25%
Class III	760	64.70%
Class IV	120	10.20%
Medical comorbidities		
Valvular heart disease	94	6.90%
Peripheral Vascular disease	167	12.20%
Hypertension	940	68.50%
Diabetes mellitus	627	45.70%
Renal failure	539	39.30%
Rheumatoid Arthritis or Collagen Vascular disease	50	3.60%
COPD	408	29.70%
Hypothyroid	282	20.60%
Obesity	228	16.60%
Anemia	449	32.70%
Substance abuse	83	6.00%
Geriatric Depression Scale		
Total score (mean, SD)	4.3	3.1
No depression	878	62.80%

Mild depression	361	25.80%
Moderate depression	119	8.50%
Severe depression	41	2.90%

Table 2.4 summarizes the distributions of the MLHFQ total, physical and emotional health scores

Table 2.4 Minnesota Living with Heart Failure Questionnaire total and subscale distribution

Subscale/scale	Mean	SD	Min	Max	25th %ile	50th %ile	75th %ile	Skewness	Kurtosis
MLHFQ total (n=944)	60.2	25.9	0	105	42	60	81	-0.2	2.3
Emotional subscale* (n=1310)	12.1	7.6	0	25	6	12	18	0	1.9
Physical subscale* (n=1272)	28.2	10.7	0	40	22	30	38	-0.7	2.6

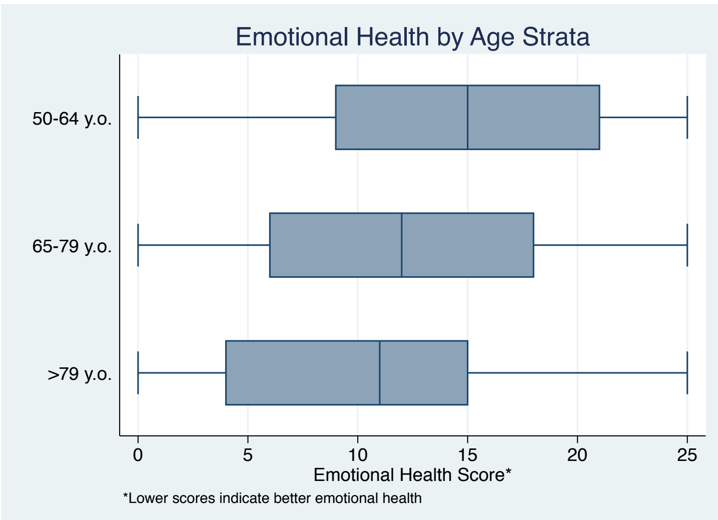
*Subscales based on factor analysis from Munyombwe, et al. Qual Life Res. 2014; 23:1753-1765. “Social/Other” subscale excluded because it is not in the standard scoring manual.
Note: a "normal" distribution has a skewness of 0 and kurtosis of 3 (approximately)

Bivariate

Individuals in the worst emotional health quantile (compared to all others) were more likely to be divorced than the other marital categories (30% vs. 23%, χ^2=5.83, p=0.016), less than 80 years old (29% vs 16%, χ^2=26.6, p<0.001), socially isolated (29% vs 23%, χ^2=4.6, p=0.03), and have worse (i.e., higher) MLHFQ physical health scores (36 vs. 23, t=-18.3, p<0.001). Those in the worst emotional health quantile were also more likely to be obese (30% vs 23%, χ^2=4.2, p=0.04) and be substance abusers (39% vs 24%, χ^2=9.2, p=0.002). There was no statistically significant association between being in the worst emotional health quantile and race/ethnicity, gender, annual household income, education status, health literacy, or other clinical variables. See Figure 2.4a for the boxplot graph of the association of emotional health scores and age.

Appendix Figure 2.4a contains other boxplot graphs displaying bivariate associations between emotional health and other variables.

Figure 2.4a Boxplot graph of association between age groups and the Minnesota Living with Heart Failure emotional health scores



Because of the hypothesis that emotional health and physical health differ by age group in the multivariable OLS regression model, I made an *a priori* decision to analyze the demographic and clinical characteristics of Beat-HF population by age to probe potential reasons for the differences (see Appendix Table 2.5). The oldest group (those >79 years old) were statistically significantly more likely to be female, non-Hispanic white, and widowed compared to the younger age groups. There was also a statistically significant higher proportion of older individuals (>79 years old) with NYHA class III heart failure, valvular heart disease, peripheral vascular disease, renal failure, hypothyroidism, and anemia. Those >79 had statistically significantly lower Lubben Social Network scores overall, suggesting more isolation, but did not have a higher proportion meeting the social isolation cutoff of 12 points on the scale.[120,122] In contrast, the oldest group was statistically significantly less likely to have obesity, be substance abusers, and have diabetes.

Construct validity analysis

Construct validity of the emotional health subscale was supported by a statistically significant correlation with the Geriatric Depression Scale ($r=0.44$, $r^2=0.19$, $p<0.001$). Figure 2.5 (in Appendix) illustrates the mean EH scores by *severe* and *less than severe* depressive symptom status; the mean EH score for those with *severe* depressive symptoms was 20.7, compared to a mean EH score of 11.9 for those with *less than severe* depressive symptoms by the GDS ($t=-6.9$, $p=<0.001$). Cohen's *d* for the mean difference in EH scores for those with severe depressive symptoms compared to those with less than severe depressive symptoms was -1.18 [bootstrapped 95% CI (-1.52, -0.84)]. This value indicates that the mean EH score for those without depression was 1.18 standard deviations *below* that of those with severe depression.

Questionnaire analysis

Cronbach's alpha was 0.93 for the 21-item total MLHFQ, 0.90 for the physical health scale, and 0.84 for the emotional health scale. Correlations of items with the physical and emotional health scales provide support for item convergence and discrimination (i.e., physical health items correlate with the physical health scale and less so with the emotional health scale and emotional health items correlate with the emotional health scale and less with the physical health scale. See Table 2.6). The physical and emotional health scales correlated 0.64 ($p<0.001$).

Table 2.6 Multitrait Multi-item Correlation Matrix for the Minnesota Living with Heart Failure Questionnaire

	Physical	Emotional
Sit	0.75*	0.53
Stairs	0.77*	0.48
Yard work	0.78*	0.53
Sleeping	0.67*	0.54
Going places	0.77*	0.57
Recreation	0.70*	0.57
Shortness of breath	0.63*	0.49
Fatigue	0.72*	0.56
Burden	0.53	0.66*
Self-control	0.58	0.72*
Worry	0.58	0.72*
Concentration	0.45	0.49*
Depressed	0.52	0.70*
Side effects	0.48	0.54
Cost	0.36	0.45
Hospital	0.57	0.52
Food	0.46	0.47
Earn living	0.40	0.39
Sex	0.46	0.46
Friends/Family	0.77	0.66

*Item-scale correlation corrected for overlap of the item with the scale score.
Note: Standard error of correlation is approximately 0.03

Missing data

597 patients (42% of the BEAT-HF population) have complete data. Eighty percent of the population are missing 5 or fewer variables. Most variables are missing less than 5%. Among non-MLHFQ variables, income is missing in 23% of the sample and NYHA class is missing in 18%. Among MLHFQ individual items, the highest percentage of missing was among the "other" scale items: "side effects" (7%), "earn a living" (12%) and "sexual activities" (18%). Though individual items in the physical and

emotional subscales are missing on average between 3-5%, the overall scale scores are only calculated with complete individual item data and, thus, have a higher percent "missing": the emotional health scale cannot be calculated in 9% of the sample and the physical health scale in 12%. See Appendix Table 2.7 for the full summary of missing variables.

Regression modeling

See Table 2.8 for the coefficients and 95% confidence intervals for the OLS model. MLHFQ emotional health was 2 points lower on average for patients >79 years old than the 50-64-year-old group [β=-1.9, 95% CI (-3, -0.8)]. Patients in the 65-79-year-old group scored approximately 1 point lower on average than the 50-64-year-old group [β=-1.2, 95% CI (-2.2, -0.2)]. For each 1-point increase on the physical health scale, emotional health scores increased by 0.4 points on average [95% CI (0.35, 0.42)]. No other covariates showed statistically significant associations with emotional health in the multivariate linear regression model. The Cook-Weisberg test for the OLS model was statistically significant, indicating heteroskedasticity. However, using regression with robust standard errors (Huber-White sandwich estimators), robust regression using iteratively reweighted least squares and controlling for clustering by hospital site, the magnitude and significance of the coefficients in the model did not change (see Table 2.8).

Table 2.8 Multivariable linear regression models for emotional health scores*

	Model 1		Model 2		Model 3		Model 4	
Variable	**Coef**	**95% CI**	**Coef**	**95% CI**	**Coef**	**95% CI**	**Coef**	**95% CI**
Age strata								
Age >79	-1.9	(-3.0, -0.8)	-1.9	(-3.1, -0.8)	-2.4	(-3.5, -1.3)	-1.9	(-3.0, -0.8)
Age 65-79	-1.2	(-2.2, -0.2)	-1.1	(-2.1, -0.1)	-1.5	(-2.5, -0.5)	-1.1	(-2.3, 0.2)
Female	0	(-0.8, 0.9)	0	(-0.9, 0.8)	-0.1	(-1.0, 0.7)	0	(-1.6, 1.6)
Race/Ethnicity								
Hispanic	-0.3	(-1.6, 1.0)	-0.4	(-1.8, 0.9)	-0.5	(-1.8, 0.8)	-0.4	(-2.2, 1.3)
Non Hispanic Black	-0.5	(-1.5, 0.5)	-0.5	(-1.6, 0.5)	-0.5	(-1.5, 0.5)	-0.5	(-2.3, 1.2)
Other race	-1.1	(-2.3, 0.1)	-1	(-2.2, 0.2)	-0.9	(-2.1, 0.3)	-1	(-2.0, 0)
Marital status								
Married	-0.2	(-1.2, 0.9)	-0.2	(-1.2, 0.9)	-0.3	(-1.4, 0.7)	-0.2	(-1.9, 1.5)
Never Married	0	(-1.2, 1.3)	0.1	(-1.3, 1.5)	-0.2	(-1.5, 1.1)	0.1	(-3.4, 3.5)
Widowed	0	(-1.2, 1.2)	0.1	(-1.1, 1.3)	0.2	(-1.0, 1.3)	0.1	(-1.4, 1.6)
Health literacy								
REALM-R<7	0.1	(-0.8, 0.9)	0.1	(-0.8, 1.0)	0.1	(-0.8, 1.0)	0.1	(-1.0, 1.3)
Annual family income								
$25-50K	0.2	(-0.7, 1.2)	0.3	(-0.6, 1.3)	0.3	(-0.7, 1.2)	0.3	(-1.8, 2.5)
$50-75K	0.9	(-0.4, 2.1)	0.8	(-0.4, 2.0)	0.6	(-0.6, 1.9)	0.8	(-0.4, 2.1)
>$75K	0.8	(-0.4, 2.0)	0.9	(-0.4, 2.1)	0.7	(-0.5, 1.9)	0.9	(-0.9, 2.6)
Social Isolation								
"Isolated" (LSNS<12)	-0.1	(-1.0, 0.8)	-0.1	(-1.1, 1.0)	0.1	(-0.9, 1.0)	-0.1	(-0.7, 0.5)
Physical Health (PH score on MLHFQ)	0.4	(0.35, 0.42)	0.4	(0.38, 0.45)	0.5	(0.42, 0.50)	0.4	(0.37, 0.47)
Medical comorbidities								
Valvular disease	0.9	(-0.6, 2.5)	1	(-0.3, 2.3)	1	(-0.6, 2.5)	1	(-0.6, 2.6)
Vascular disease	0.1	(-1.0, 1.3)	0	(-1.2, 1.2)	0.2	(-1.0, 1.3)	0	(-1.4, 1.4)
COPD	0.2	(-0.7, 1.0)	0.1	(-0.8, 0.9)	0.1	(-0.7, 0.9)	0.1	(-0.7, 0.8)
Diabetes	0.1	(-0.7, 0.9)	0.2	(-0.6, 1.0)	0.2	(-0.5, 1.0)	0.2	(-1.0, 1.4)
Renal disease	-0.4	(-1.2, 0.4)	-0.3	(-1.1, 0.5)	-0.3	(-1.1, 0.5)	-0.3	(-1.5, 0.9)
Hypertension	0.1	(-0.7, 0.9)	0.1	(-0.6, 0.9)	0.3	(-0.5, 1.1)	0.1	(-1.6, 1.9)
Hypothyroid	0.8	(-0.1, 1.8)	0.9	(-0.1, 1.8)	0.9	(0, 1.9)	0.9	(0.2, 1.6)
Rheumatoid arthritis	0.7	(-1.3, 2.7)	0.7	(-1.3, 2.7)	0.8	(-1.1, 2.8)	0.7	(-2.0, 3.3)
Obesity	0.3	(-0.7, 1.3)	0.5	(-0.6, 1.6)	0.3	(-0.7, 1.3)	0.5	(-0.7, 1.6)
Anemia	0.9	(0.1, 1.7)	0.9	(0.1, 1.8)	1	(0.1, 1.8)	0.9	(0.5, 1.4)
Substance abuse	1.2	(-0.5, 2.8)	1	(-0.6, 2.7)	0.8	(-0.8, 2.4)	1	(-0.9, 2.6)

*Model 1: OLS multivariate regression
Model 2: Regression with robust standard errors (Huber-White Sandwich method)
Model 3: Robust linear regression with iterative weights
Model 4: Robust regression controlling for clustering by hospital (6 hospital sites: UCD, UCI, UCLA, Cedars-Sinai, UCSD, UCSF)
Reference categories for model: age 50-64, white race/ethnicity, divorced marital status, and <$25K family income

Table 2.9 shows the coefficients in the main model in parallel with the 2 models utilized for the sensitivity analysis:

- model 1: complete-case analysis (as in Table 2.8, Model 1)
- model 2: limited regression model that includes only variables with minimal missing values (less than 3%), and
- model 3: limited regression model including variables whose coefficients in the complete-case multivariable model that have a p-value<0.20.

Table 2.9 Sensitivity analysis: comparison of regression coefficients across models for emotional health scores*

	Model 1		**Model 2**		**Model 3**	
Variable	**Coeff**	**95% CI**	**Coeff**	**95% CI**	**Coeff**	**95% CI**
Age strata						
Age >79	-1.9	(-3, -0.8)	-4.2	(-5.4, -3.1)	-1.9	(-2.8, -1.0)
Age 65-79	-1.2	(-2.2, -0.2)	-2.4	(-3.4, -1.4)	-1	(-1.9, -0.2)
Female	0	(-0.8, 0.9)	0.2	(-0.7, 1.0)		
Race/Ethnicity						
Hispanic	-0.3	(-1.6, 1.0)	-0.6	(-2.0, 0.7)		
Non Hispanic Black	-0.5	(-1.5, 0.5)	-1.4	(-2.5, -0.3)		
Other race	-1.1	(-2.3, 0.1)	-1.3	(-2.6, 0.3)		
Marital status						
Married	-0.2	(-1.2, 0.9)	-0.3	(-1.4, 0.8)		
Never Married	0	(-1.2, 1.3)	-0.1	(-1.5, 1.4)		
Widowed	0	(-1.2, 1.2)	-0.1	(-1.4, 1.2)		
Health literacy						
REALM-R<7	0.1	(-0.8, 0.9)				
Annual income						
$25-50K	0.2	(-0.7, 1.2)				
$50-75K	0.9	(-0.4, 2.1)				
>$75K	0.8	(-0.4, 2.0)				
Social Isolation						
"Isolated" (LSNS<12)	-0.1	(-1.0, 0.8)				

Physical Health (PH score on MLHFQ)	0.4	(0.35, 0.42)		0.43	(0.40, 0.47)
Medical comorbidities					
Valvular disease	0.9	(-0.6, 2.5)		0.8	(-0.5, 2.2)
Vascular disease	0.1	(-1.0, 1.3)			
COPD	0.2	(-0.7, 1.0)			
Diabetes	0.1	(-0.7, 0.9)			
Renal disease	-0.4	(-1.2, 0.4)			
Hypertension	0.1	(-0.7, 0.9)			
Hypothyroid	0.8	(-0.1, 1.8)		0.8	(-0.02,1.7)
Rheumatoid arthritis	0.7	(-1.3, 2.7)			
Obesity	0.3	(-0.7, 1.3)		-0.2	(-1.1, 0.7)
Anemia	0.9	(0.1, 1.7)		0.5	(-0.2, 1.2)
Substance abuse	1.2	(-0.5, 2.8)		1.2	(-0.3, 2.6)

*Model 1 is the complete case model where cases with missing data are dropped from the model. Model 2 includes variables with minimal missing data. Model 3 limited to variables with p-values<0.2

See Table 2.10 in the Appendix for the quantile regression coefficient table (higher quantiles indicate worse emotional health). In the quantile regression models, age and physical health were still statistically significant. The association between older age and better emotional health (i.e., smaller EH scores) appeared strongest at the 75th quantile of emotional health [β=-2.7, 95%CI (-3.7, -1.7)], but the difference in association across quantiles was not significant (i.e., the F test for difference in coefficients between the 75th quantile and the 25th was not statistically significant). The association between physical health and emotional health did vary across extreme ends of the quantiles; at the 75th quantile of emotional health a one-point increase in physical health was associated with a 0.5-point increase in emotional health score, while at the 10th quantile of emotional health a one-point increase in physical health was associated with a 0.2-point increase in emotional health. The difference between the coefficients was statistically significant (F=90.47, p<0.001). Appendix Figure 2.6 shows the individual graphs for each variable coefficient in the quantile regression model.

After imputation, re-estimation of the regression model demonstrated that coefficients were consistent (in magnitude, direction and significance) with the non-imputed model. See Table 2.11 below for the coefficients and 95% confidence intervals in the regression model after multiple imputation.

Table 2.11 Multiple imputation regression model coefficients for emotional health scores

Variable	Coeff	95% CI
Age strata		
Age >79	-2.3	(-3.7, -1.0)
Age 65-79	-1.1	(-2.1, -0.1)
Female	-0.5	(-2.3, 1.2)
Physical Health (PH score on MLHFQ)	0.4	(0.41, 0.47)
Medical comorbidities		
Valvular disease	1.1	(-1.2, 3.4)
Vascular disease	0	(-1.4, 1.4)
COPD	-0.2	(-1.1, 0.6)
Diabetes	0.7	(-0.3, 1.8)
End stage kidney disease	-0.2	(-2.0, 1.6)
Hypertension	0.1	(-1.2, 1.5)
Hypothyroid	0.9	(-0.3, 2.2)
Rheumatoid arthritis	0	(-3.0,3.0)
Obesity	-0.2	(-1.1, 0.8)
Anemia	0.6	(-0.7, 1.9)
Substance abuse	0.7	(-3.2, 4.6)

Not all variables shown in table: MI regression model controls for age, race, gender, education, marital status, income, physical health, and medical comorbidities.
n=1309 for multiple imputation regression model. F=36.8, p<0.0001

In the mixed effects linear model using maximum likelihood estimation and controlling for patient-level random effects, the oldest age group (>79) had emotional health scores 1.2 points lower than the youngest group (50-64 y.o.) accounting for the fixed effects of time, treatment group, demographics and clinical characteristics and individual-level random effects [β =-1.2, 95%CI (-1.9, -0.5)]. The LR test for the mixed model with patient level random intercepts was statistically significantly better than the OLS model (LR test vs. linear model χ^2=125.1, P<0.00001). See Table 2.12 below for the mixed effects model coefficients.

Table 2.12 Mixed effects linear regression model coefficients for emotional health scores (with patient level random effects)

Variable	Coeff	95% CI
Age strata		
Age >79	-1.2	(-1.9, -0.5)
Age 65-79	-1	(-1.6, -0.3)
Female	0	(-0.5, 0.6)
Race/Ethnicity		
Hispanic	0.5	(-0.3, 1.4)
Non-Hispanic Black	-0.1	(-0.8, 0.6)
Other race	-0.4	(-1.1, 0.4)
Marital status		
Married	0.1	(-0.6, 0.8)
Never Married	0	(-0.9, 0.9)
Widowed	0	(-0.9, 0.7)
Health literacy		
At risk for poor health literacy (REALM-R<7)	0.1	(-0.5, 0.7)
Annual household family income		
$25-50K	-0.2	(-0.8, 0.5)
$50-75K	-0.2	(-1.0, 0.6)
>$75K	-0.1	(-0.9, 0.7)
Social Isolation		
"Isolated" (LSNS<12)	0.5	(-0.2, 1.1)
Physical Health (PH score on MLHFQ)	0.4	(0.38, 0.42)
Medical comorbidities		
Valvular disease	0.1	(-0.9, 1.2)
Vascular disease	0.3	(-0.4, 1.1)
COPD	-0.2	(-0.7, 0.4)
Diabetes	0.2	(-0.4, 0.7)
End stage kidney disease	-0.6	(-1.1,- 0.04)
Hypertension	-0.2	(-0.7, 0.3)
Hypothyroid	0.6	(-0.03, 1.2)

Rheumatoid arthritis	-0.9	(-2.2, 0.4)
Obesity	-0.2	(-0.8, 0.5)
Anemia	0.5	(-0.01, 1.1)
Substance abuse	0.3	(-0.8, 1.4)
Treatment	-0.2	(-0.7, 0.3)
Time		
7 days	-2.3	(-2.8, -1.7)
30 days	-1.9	(-2.5, -1.4)
180 days	-1.9	(-2.5, 1.4)

A mixed model incorporating patient-level random slopes (i.e., different patterns for emotional health over time) was not statistically significant compared to the random intercept model (X^2=1.8, P=0.18). The LR test comparing the random slopes model with unstructured covariance to the random intercept model alone is not significant (χ^2=1.96, P=0.37)

The LR test for the mixed model with hospital level random intercepts was statistically significantly better than the OLS model (LR test vs. linear model χ^2=6.84, P=0.0045). See Appendix Table 2.13 for the mixed effects model coefficients with hospital level random effects. A model accounting for hospital level random slopes was not statistically significantly better than the random intercept model alone (χ^2=0.14, P=0.71). The LR test comparing the hospital level random slopes model with unstructured covariance to the random intercept model alone was statistically significant (χ^2=8.75, P=0.01).

After imputation, re-estimation of the mixed effects regression models demonstrated that coefficients were consistent (in magnitude, direction and significance) with the non-imputed mixed effects models.

Mediation and structural equation models

Social isolation was not significantly uniquely associated with emotional health when included in the multivariable model, so only physical health was analyzed as a potential mediator. Table 2.14 lists the regression coefficients for the primary mediation model ("seemingly unrelated regression") which keeps the age variable as categorical. The table also details the indirect effects of each age stratum on emotional health (through the physical health pathway), the direct effects of age on emotional health, and the bias corrected bootstrapped 95% confidence intervals for each of the pathways. The indirect effect of age 65-79 on the outcome is a1*b=-2.78(0.43) =-1.20. For age>79 it is a2*b=-3.9(0.43) =-1.68. The total indirect effect is the nonlinear combination of each separate pathway: a1*b+a2*b=-2.88. The bias corrected 95% confidence intervals are statistically significant in each of the pathways. Fifty percent of the direct effect of age on emotional health is mediated by physical health [indirect/(indirect+direct)]*100=-2.88/(-2.88-2.87)*100=50.1%]. This is consistent with the Sobel-Goodman mediation test, which showed that 49% of the effect of age on emotional health was mediated through physical health.

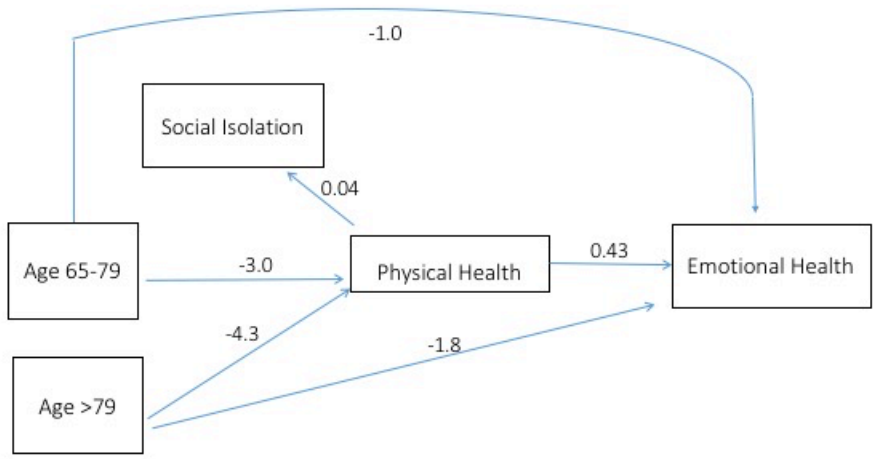
Table 2.14 Coefficients from "seemingly unrelated regression" model with direct and indirect effects of age on emotional health with bootstrapped bias corrected 95% Cis

	Coefficient	**Corresponding path in figure 2.2**
Column1	**Column2**	**Column3**
Physical health outcome (mediating variable)		
Age category		
65-79	-2.78	*"a1"*
>79	-3.9	*"a2"*
Socially isolated	3.59	
Hypothyroid	0.37	
Substance abuse	0.34	
Anemia	0.21	
Obesity	3	

Emotional health outcome		
Physical health	0.43	*"b"*
Age category		
65-79	-1	*"c1"*
>79	-1.87	*"c2"*
Socially isolated	-0.15	
Hypothyroid	0.77	
Substance abuse	1.14	
Anemia	0.62	
Obesity	-0.05	
Indirect and direct effects		**Bias corrected bootstrapped 95% CIs**
Age 65-79*physical health	-1.2	(-1.87, -0.55)
Age >79*physical health	-1.68	(-2.37, -1.01)
Total **indirect** effect of age on emotional health	-2.88	(-4.06, -1.70)
Total **direct** effect of age on emotional health	-2.87	(-4.41, -1.33)

Figure 2.7 displays the generalized structural equation model showing the relationships between age, social isolation, physical health and emotional health (age as categorical and social isolation as dichotomous). In this model age was not associated with the dichotomous outcome of social isolation. Older age is associated with better physical and emotional health scores (i.e., lower scores or negative coefficients in the gsem model). In addition, physical health was associated with a small, but statistically significant higher odds of social isolation [coeff=0.04, 95%CI (0.02, 0.06)].

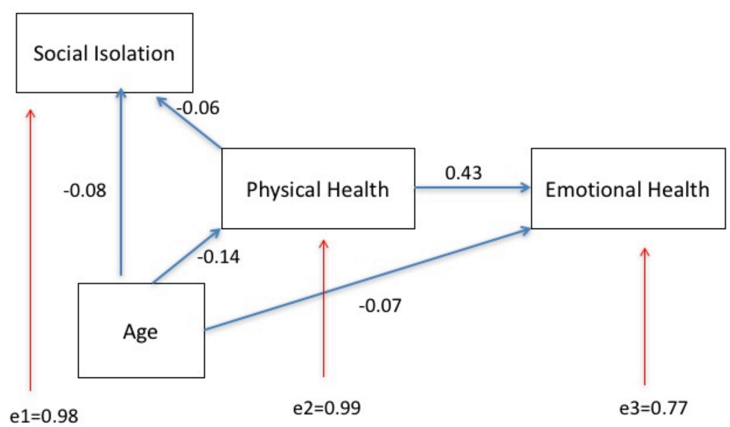
Figure 2.7 Generalized Structural Equation Model: relationships between age, physical health, social isolation and emotional health*



**Coefficients for the GSEM model are not standardized and age and social isolation variables are categorical. Coefficient for physical health on outcome of social isolation is on log odds scale (Odds ratio=$e^{0.04}$=1.04).*

See Figure 2.8 for additional structural equation models ("pathreg" and "sem" controlling for clustering) with standardized coefficients. The "pathreg" model (with age and social isolation as continuous variables) indicates that a one standard deviation increase in age is associated with a -0.08 standard deviation change in the Lubben Social Network score (i.e., older age associated with lower LSNS scores). A one standard deviation increase in age is also associated with a -0.14 standard deviation change in physical health score (i.e., older age associated with lower/better physical health scores). A one standard deviation increase in age is also associated with a -0.07 standard deviation change in emotional health score (i.e., older age associated with lower/better emotional health scores). A one standard deviation increase in physical health score is associated with a -0.06 standard deviation change in LSNS score (i.e., worse physical health is associated with lower social isolation scores). The structural equation model accounting for clustering by hospital site (using STATA's *sem* notation) was consistent with the structural equation model without clustering in figure 2.8 (using STATA's *pathreg* notation).

Figure 2.8 Structural equation model for age, physical health, social isolation and emotional health*



**Model uses STATA pathreg notation. All coefficients are standardized and variables for age and social isolation are continuous. All coefficients significant at p<0.05 except for coefficient between social isolation and emotional health.*

Discussion

Among patients in the BEAT-HF trial, older age was associated with better emotional health on the MLHFQ. The magnitude and significance of this association was consistent across regression models (OLS, OLS with robust standard errors, robust linear regression with iterative weights, quantile regression, regression after multiple imputation, and mixed effects linear regression). In addition, this analysis lends support to the hypothesis that physical health may partially mediate the relationship between age and emotional health in this heart failure population.

Several relationships run counter to my original hypotheses. I proposed that older age would be associated with worse emotional health due to increased limitations, frailty and social isolation. But in this sample older age may have been associated with better emotional health because of *better* self-perception of physical health, less frailty or because of increased coping with limitations compared to younger heart failure patients. Interestingly, there was a higher proportion of nearly every major comorbidity in the oldest age group which would suggest potentially *more* physical limitations and frailty on average despite the better self-reports of health with increasing age. We do not have information on the severity of other comorbidities, but there was a higher proportion of NYHA class III CHF in older than younger individuals. The oldest age group also had more social isolation on the continuous Lubben Social Network score, but they were not more likely to be classified as "socially isolated" on the LSNS≤12 points threshold. Despite these differences (and after controlling for these differences) the oldest patients in this trial were more likely to report better physical and emotional health. This may reflect coping. The literature gives some support to the coping hypothesis, as some small studies have found a greater sense of coherence in older heart failure patients (as measured by a validated questionnaire looking at meaningfulness and manageability of one's circumstances) compared to a healthy age-matched cohort[134]. Thus, it's possible that emotional health is better in older patients in this trial because of their ability to derive meaning from their illness and/or better manage their illness. I also did not discover a statistically significant relationship between the proportion of older individuals socially isolated as compared to younger patients with heart failure, so it is possible that emotional health might be worse for a different heart failure population where older individuals had more isolation. Given that the older heart failure patients in this trial are more likely to be white and female, it is also possible that we are simply identifying a "healthier" older phenotype of mostly diastolic heart failure patients that may have improved self-perception of disease (we do not, however, have accurate information on ejection fraction in the BEAT-HF trial). Survivor bias also must be considered, both in the results of the cross-sectional baseline analysis and in the longitudinal analysis. Those older patients who entered the study at baseline may have already survived with heart failure for a longer period of time than the younger patients. It is possible that the older patients with worse HRQOL died and were excluded from the study (selection effect). In the longitudinal analyses, older patients who survived during the study period may have artificially augmented the difference in scores between young and old.

In addition to better emotional health in older patients in the BEAT-HF trial, I surprisingly discovered better self-reported physical health in older patients. This runs counter to other heart failure populations, but again it may be that there was less frailty or physical limitations in the elderly BEAT-HF population compared to other studies.[135] In one small study younger patients had better physical symptom status (defined by a dyspnea-fatigue index score), but despite these better physical symptoms younger patients reported *worse* HRQOL (i.e., MLHFQ total score) in adjusted analyses. [109] The results from other small studies are challenging to compare given different methods and populations, but the raw scores on MLHFQ were similar or even worse in the BEAT-HF population indicating that the hospitalized BEAT-HF group did not appear to be “healthier”. Thus, the improved self-reported physical health scores in the older population—again—may be a sign of improved coping in this population. [70,136,137] Also, given that those studies were in an extremely small subsample of heart failure patients it may be that the BEAT-HF patients are more representative of the larger heart failure population.

This study has several potential limitations. The use of a health-related quality of life survey opens up a potential for non-response bias (i.e. people who complete the survey are different from the people who don’t) which could potentially alter the relationship between age and emotional health. Beyond non-response bias, my analyses are conducted in a way that breaks up the initial randomization, which opens up the possibility of residual confounding even after controlling for major covariates. IN mixed effects modeling (using all time points) there may be residual confounding by treatment group despite controlling for treatment in the model. With regard to structural equation modeling, it is possible that the effects along the various paths are not unidirectional (i.e. the model may be non-recursive) altering the true relationships along the various paths. In addition, it is important to note the limitation of the construction of emotional health in this study based on a numerical score. Emotional health is complex, thus a numerical score on the MLHFQ likely does not encapsulate all aspects of emotional health. Survivor bias may have also altered the study results, but given the equivalent baseline emotional subscale scores between those who died and those who survived it is challenging to determine the possible effect on the outcome. Finally, though this is a large trial it was limited to California hospitals and the participants may not be representative of the larger national heart failure population.

Despite these limitations, the study controls for major threats to internal validity. First, the BEAT-HF population had a low non-response or missing rate of approximately 2% or less on most questions for the baseline survey. In regards to breaking up randomization, the analyses control for major confounders and multiple models show a consistent effect for age differences in emotional scores (both in cross-sectional analyses and longitudinal analyses). In addition, all mediation models showed consistent associations (magnitude, direction and proportion of mediation by physical health) which provides additional layers of support to the findings. Importantly, this is one of the largest heart failure trials evaluating HRQOL, incorporating data from both academic centers and safety-net hospital, thus, the findings may be more representative of the relationships between age, physical health and emotional health than other smaller studies.

Conclusion

This study adds to the literature in important ways: (1) provides a targeted evaluation of differences in emotional health by age group using the emotional dimension scores in the MLHFQ in a large heart failure population and (2) explores and confirms the complex role of physical health in mediating the association between age and emotional health. Given the national focus on patient reported outcomes (PROs) from the National Institutes of Health, the Agency for Healthcare Research and Quality and the Centers for Medicare and Medicaid Services combined with the growing burden of heart failure in the US population, this analysis is timely and provides additional information about an important aspect of patient health in heart failure.[45,138–140]

Chapter 3

Effects of Telemonitoring and Nurse Coaching on Emotional Health Among Heart Failure Patients

This chapter explores the following three questions:

Question 3a: Does a telemonitoring and nurse coaching intervention impact emotional health in heart failure patients?

Question 3b: Does the association between the intervention and emotional health vary by social isolation?

Question 3c: Does the association between the intervention and emotional health vary by age group?

Background

Chapter 2 detailed heart failure's impact on HRQOL. As noted, mental (emotional) health is an important aspect of HRQOL. The main BEAT-HF trial results demonstrated that the telemonitoring and nurse coaching intervention positively effected MLHFQ total score at 180 days.[115] But two additional questions remain: does the intervention improve emotional health, and is there a differential effect of treatment on certain subgroups? [141,142]

Monitoring and education programs in heart failure

The role of telemonitoring (TM) and nurse coaching/structured telephone support (STS) in heart failure patients has been evaluated in numerous studies, examining the potential role in reducing hospital readmissions, mortality and improvements in HRQOL. Inglis and colleagues conducted a systematic review and meta-analysis of the broad range of benefits TM and STS provide for heart failure patients.[143] They found that trials generally supported a positive effect of TM and STS on all-cause mortality [RR=0.66, 95%CI (0.54-0.81)], reducing CHF-related hospitalizations [RR=0.79, 95%CI (0.67-

0.94)] and improving HRQOL.[143] Examining the specifics of some of the trials is important: A small single-site trial of nurse education and telemonitoring in heart failure found significant mortality reductions in heart failure patients.[144] However, a larger multi-site trial evaluating telemonitoring found no decrease in death or readmission for heart failure.[145] Interestingly, in this larger study, the intervention did not include education, coaching or peer support (which may have been the reason for the positive results in the previous smaller trial). Importantly, the main BEAT-HF trial results now show that in a large study with TM and STS there was no improvement in all-cause mortality at 180 days nor all-cause readmission at 180 days.[115]

With regard to the effects of telemonitoring and education on HRQOL, studies have been mixed. Several studies have shown that structured telephone support (STS) may improve scores on disease-targeted HRQOL measures.[146,147] Another telephone support intervention that focused on heart failure patients of Hispanic ethnicity found no difference in HRQOL (using both generic and disease-targeted HRQOL measures).[148] However, none of these studies reported the effects of STS specifically on emotional health, an important and potentially modifiable outcome in heart failure patients.[76–78,92,97] Again, the main BEAT-HF trial found a small but statistically significant effect of the intervention on MLHFQ total score, but the specific effects on the subcomponent of emotional health have not been evaluated.[115]

The effect of nurse education for patients with chronic illness may be mediated through the frequency and quality of contact with physicians and nurses, which can improve satisfaction with care, self-care and adherence to medications.[149–151] In a study of 90 heart failure patients in one center, increased contact with a heart failure nurse improved patient satisfaction with care but did not significantly change the MLHFQ total score over a 6 month period.[152] While not strictly focused on nurse education, other observational studies have shown that educational and cardiac rehabilitation interventions improve scores on disease-targeted HRQOL measures.[153–155]

Social isolation, aging and heart failure

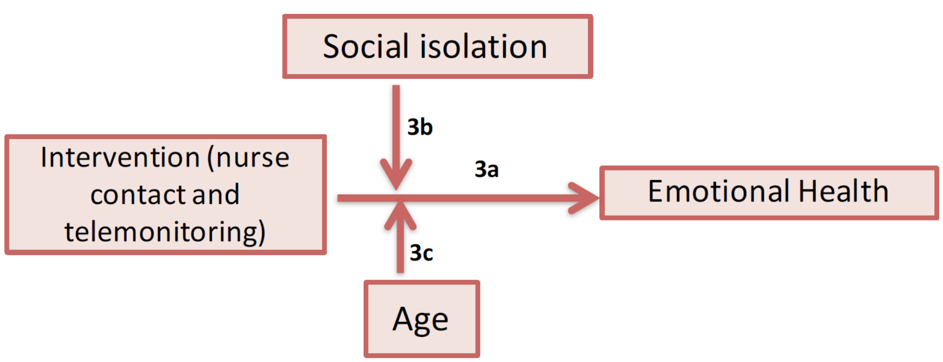
Educational, telemonitoring and disease-management programs could potentially have different effects on patients depending on their receptivity to the intervention. Specifically, as heart failure patients age, they typically have increases in comorbidities, number of prescription medications, and level of frailty.[67,81,156–159] All of these factors may increase the need for—and receptivity to—increased disease management through monitoring or coaching.[160,161] Some individuals with chronic disease may be receptive to teaching and monitoring if they feel it will improve communication with their providers.[162] Social isolation may also increase the receptivity to monitoring programs, as one telemonitoring program showed improvement in depressive symptoms in home-bound isolated older adults.[163]

Given that nurse coaching has been shown to improve total MLHFQ scores,[115] it is important to examine the role of telemonitoring and nurse coaching in improving emotional health specifically. Moreover, it is critical to evaluate whether such a program has a differential effect on subgroups of heart failure patients—notably the oldest and the most socially isolated. Thus, whereas chapter 2 detailed the differences in emotional health across the aging spectrum, this chapter will assess the effectiveness of a nursing intervention in a large and diverse heart failure sample—adding to our knowledge of the effectiveness of TM and STS on emotional health.

Conceptual model

The primary relationship being assessed is the association between the intervention (telemonitoring and nurse coaching) and emotional health (Figure 3.1, arrow 3a). An additional relationship of interest is the potential modifying role (i.e., differential treatment effect) that social isolation may play on the associations between the intervention and emotional health (Figure 3.1, arrow 3b). Finally, the model highlights the potential modifying role of age on the intervention's impact on emotional health (Figure 3.1, arrow 3c).

Figure 3.1 Conceptual Model



Given that patients were randomized to the intervention (monitoring and nurse coaching), the covariates should be balanced across the two trial arms. However, it is possible that some factors may be unevenly distributed across the nurse coaching intervention and associated with the outcome (emotional health). The individual factors (gender, race/ethnicity, education, comorbid burden) and environmental factors (healthcare access, income, insurance) are not included in the conceptual model because they are assumed to be balanced in the randomized design, but they have been discussed in chapter 2.

I've already highlighted many of the relationships with the above variables as they relate to emotional health, so I will limit my discussion to the potential modifying role of age and social isolation on the relationship between the intervention and emotional health. Older patients potentially have a more heightened sense of need for education and a readiness to change health behaviors that impact heart failure symptoms (i.e. salt and fluid restriction) and potentially emotional health (less worry about heart failure and more self-control compared to younger patients over time). Socially isolated individuals may also have a heightened desire for contact with healthcare workers, making the intervention more effective in this subgroup and changing emotional health to a greater extent than in a non-isolated subgroup.

Methods and Measures

Data Source

As in Chapter 2, I utilize the data from the BEAT-HF clinical trial.

Measure construction and definition

See Table 3.1 for the list of concepts, variables, and construction. The table contains additional detail on justifications and limitations.

Table 3.1 Concepts and measures

Concept	Variable	Variable construction	Justification	Limitations
Main Outcome				
Emotional Health	EH score from 4 time points (0, 7, 30, and 180 days)	Continuous variable at 4 time points based on answers to 5 questions on the emotional subscale of the MLHFQ.	Using 4 time points to assess the role of the intervention on changes in EH.	MLHFQ administered face-to-face at baseline and via telephone at all other time points. Test-retest reliability between these two modes of administration>0.85.
Primary predictor				
Provider-patient communication (telehealth intervention: contact with health care providers)	Intervention/Treatment	ITT analysis: treatment=0/1	Increased monitoring and contact with nurse coaching more likely to increase EH through less worry, improvements in self-confidence in care, patient empowerment	If difference found, challenging to determine which component of the intervention may be responsible.
Moderating variables				
Multidimensional: coping, physical changes, frailty	Age	Dummy encoded for three age strata: Age 50-64, 65-79, and >79. Reference category will be 50-64 age group.	Changes with age may moderate the effect of nurse contact on the outcome of EH	Loss of variability in using age-strata. May miss finer associations between changes in age and EH
Isolation	Social network scale	Continuous variable as defined by score on the Lubben Social Network Scale-6 (scored 0-30 overall based on 6 items about family and friends). Will also use dichotomous 12-point cutoff that has been used in the literature to define "isolation"	Socially isolated individuals may respond differently to the intervention. Social isolation is a key theoretical driver of EH.	Using a cutoff point may miss finer associations with EH. Shorter 6 item questionnaire does not encapsulate all aspects of social isolation.
Other covariates				
Access	Insurance	Insured=1, uninsured=0	.	.
	Household income	Four dummy encoded categories (1/0): Household income <25K, 25-50K, 50-75K, >75K.	.	.
Intrinsic characteristics	Gender	Dichotomous: Male=1, Female=0	.	.
	Education	Three dummy encoded categories: Less that high school, high school grad, and college grad	.	.

	Race/ethnicity	All dummy encoded (1/0): Hispanic, Non-Hispanic White, Non-Hispanic Black, Other Race. Non-Hispanic White is reference group.	.	.
	Health Literacy	Score on REALM-D: Dichotomous variable based on score <6 indicating "at risk for poor health literacy"	.	.
Functional status	NYHA functional class (I-IV)	Heart failures broken down into three groups: (1)class I-II, (2)class III, and (3)class IV	.	.
	Comorbidity variables: MI (prior heart attack), CVA (stroke), DM (diabetes), COPD (Chronic obstr lung disease), ESRD	Dichotomous variables (other than creatinine) based on ICD-9 codes on admission.	.	.
	Depression	Scores on Geriatric depression scale. Will utilize as continuous variable and as categorical: (1) no depression (0-4), (2) mild depressive sxs (5-8), (3) moderate depressive sxs (9-11), and (4) severe depressive sxs (>11 points).	.	.

Below is the list of variables:

Outcome variable

The outcome variable is the same for this study as prior chapter: the MLHFQ emotional health subscale. I utilize questionnaire data from four time points: baseline, 7 days, 30 days and 180 days. These time points were chosen to examine the full effect of the intervention (total nurse contact over the study period). The baseline survey was administered as a face-to-face interview with study staff prior to randomization. Follow-up surveys were administered via nurse telephone interview. Test-retest reliability between face-to-face and telephone administration was 0.87 in one study.[164]

Primary predictor

- The primary predictor is treatment arm.

Moderating variables

- Age is constructed in three groups: 50-64 years old, 65-79 years old and >79 years old.
- Social isolation: As in the prior analysis, a social isolation "cutoff" of 12-points or below is used to categorize those as isolated.[120,122]

Covariates

The covariates for this project are the same as for Chapter 2, but are only adjusted for in regression models if they are imbalanced across treatment arms in bivariate analyses.

Statistical methods

Bivariate analysis

Bivariate relationships between the intervention arm and covariates are assessed with the χ^2 test for categorical variables and the t-test for continuous variables. Differences between mean MLHFQ scores (total, physical and emotional health scales) by age group are assessed using one-way ANOVA.

I examine bivariate relationships among those with any missing survey data vs. those with complete (i.e., no missing) survey data at 180 days. In addition, I examine differences among those with completely missing survey data and those with some or no missing survey data.

Missing data imputation methods

I utilize multiple imputation with chained equations, as in Chapter 2. However, in the main analysis I do not impute data for those individuals known to be deceased. For the main regression analyses I do not impute outcome data, but in sensitivity analyses I impute missing emotional health scores if individuals have at least 2 out of the 5 questions completed. I conduct an additional sensitivity analysis by imputing physical and emotional health scores at the worst possible value (EH=25, PH=40) for those known to be deceased at the time of data collection. Other methods imputing scores using predicted probabilities based on timing of death have been done in other studies, but were not done in this analysis because of the timing of data collection and uncertainty about time of death in the BEAT-HF trial.[165]

Regression analyses

Research question 3a: Does the intervention impact emotional health in heart failure patients?

First, an intention to treat analysis is performed that respects the randomization process. I use a mixed effects regression model to assess the intervention group and time interaction:

Y (emotional dimension score)_t= β0 +β1(treatment group) + β2-β4(time) **+β5-β10(treatment group)(time)** + βj (covariates) +ε_I

Time is treated as categorical in this model given the nonlinear change in emotional health scores over time. The model adjusts for patient-level and hospital-level random effects. In addition, it controls *only* for those covariates that are shown to be significantly imbalanced across treatment arms in bivariate analysis.

Research question 3b: Does the association between the intervention and emotional health vary based on social isolation?

An intent to treat analysis is performed using mixed effects linear regression. The coefficient of interest in the model is the interaction term that includes randomization group, time, and social isolation. Again, only those covariates that are imbalanced with respect to the intervention are controlled for as in the first model.

Research question 3c: Does the association between the intervention and emotional health vary by age group?

The analysis will mirror that in question 3b. An initial intent to treat analysis is performed using mixed effects linear regression. The coefficient of interest in the model is an interaction term that includes randomization group, time, and age. Only those covariates that are imbalanced with respect to the intervention will be controlled for as in the first model.

Sensitivity analyses

Sensitivity analysis will be conducted as noted above: A multiple imputation model that imputes deceased scores as the worst possible (EH=25) and an imputation model that imputes EH scores for those with at least 2 out of 5 complete. These analyses will allow for the incorporation of more outcome data and increase the sample size. Given the reliability and validity of actual emotional health scores in the deceased are unknown, as are the total scores for those with incomplete scale items, these analyses are secondary.

Results

The univariate characteristics of the BEAT-HF population were presented in Chapter 2 (Table 2.3). The characteristics of the BEAT-HF population by treatment group are presented in Table 3.2.

Table 3.2 Baseline characteristics of the BEAT-HF population by treatment arm*

	Usual Care (n=722)	Intervention (n=715)
Age		
>79	247 (34.2%)	266 (37.2%)
65-79	271 (37.5%)	236 (33.0%)
50-64	204 (28.3%)	213 (29.8%)
Gender		
Female	331 (45.9%)	333 (46.6%)
Race/ethnicity		
Hispanic	78 (10.9%)	85 (12.0%)
Non-Hispanic Black	163 (22.7%)	153 (21.5%)
Non-Hispanic White	390 (54.3%)	389 (54.7%)
Other race	87 (12.1%)	84 (11.8%)
Marital status		
Married	291 (41.8%)	294 (42.1%)
Divorced	152 (21.8%)	166 (23.8%)
Widowed	170 (24.4%)	162 (23.2%)
Never married	84 (12.1%)	76 (10.9%)
Education		
Less than high school	101 (14.5%)	111 (15.9%)
High school graduate	373 (53.7%)	355 (50.9%)
College graduate	221 (31.8%)	232 (33.2%)
Health literacy		
At risk for poor health literacy (no. and % with REALM-R<7)	204 (28.9%)	224 (31.6%)
Annual household family income		
<$25 K	223 (40.8%)	220 (39.2%)
$25-50K	147 (26.9%)	138 (24.6%)
$50-75K	85 (15.5%)	78 (13.9%)
>$75K	92 (16.8%)	126 (22.4%)

Social isolation		
Lubben social network Scale score (mean, SD)	17.2 (6.9)	17.2 (6.5)
"Isolated" (no. and % with LSNS<12)	145 (21.1%)	147 (21.4%)
NHYA class		
Class I-II	154 (26.5%)	140 (23.6%)
Class III	371 (63.9%)	389 (65.6%)
Class IV	56 (9.6%)	64 (10.8%)
Medical comorbidities		
Valvular heart disease	51 (7.4%)	43 (6.3%)
Peripheral Vascular disease	77 (11.1%)	90 (13.3%)
Hypertension	467 (67.4%)	473 (69.7%)
Diabetes mellitus	326 (47.0%)	301 (44.3%)
Renal failure	284 (41.0%)	255 (37.6%)
Rheumatoid Arthritis or Collagen Vascular disease	22 (3.2%)	28 (4.1%)
COPD	210 (30.3%)	198 (29.2%)
Hypothyroid	141 (20.4%)	141 (20.7%)
Obesity	114 (16.5%)	114 (16.8%)
Anemia	222 (32%)	227 (33.4%)
Substance abuse	38 (5.5%)	45 (6.6%)
Geriatric Depression Scale		
Total score (mean, SD)	4.3 (3.1)	4.3 (3.2)
No depression	434 (62.2%)	444 (63.3%)
Mild depression	189 (27.1%)	172 (24.5%)
Moderate depression	58 (8.3%)	61 (8.7%)
Severe depression	17 (2.4%)	24 (3.4%)

**There is no statistically significant difference in clinical characteristics or demographics between treatment groups*

The MLHFQ scores over time by treatment group are presented in Table 3.3 and Appendix Figure 3.2. In unadjusted comparisons, the intervention arm had lower mean MLHFQ total scores at 180 days [Usual care mean score= 31.8 vs. Intervention mean score= 28.0, t=1.9, $P<0.05$], physical health subscale [usual care mean score =16.5 vs. Intervention mean score=14.9, t=1.75, $P<0.05$], and emotional health subscale [Usual care mean score = 6.4 vs. Intervention mean score = 7.1, t=2.3, $P<0.01$].

Table 3.3 MLHFQ scores over time by treatment arm

		Mean score (SD) at time point			
		Baseline	**7 days**	**30 days**	**180 days**
Usual care	Total MLHFQ	60.0 (25.7)	29.5 (26.8)	31.5 (26.6)	31.8 (27)
	Physical health	28.5 (10.5)	15.6 (12.6)	16.2 (12.5)	16.5 (12.9)
	Emotional health	12.2 (7.5)	5.3 (7.2)	6.1 (7.2)	6.4 (7.7)
Intervention	Total MLHFQ	60.5 (26.2)	26.2 (25.1)*	30.0 (26.7)	28.0 (24.2)*
	Physical health	27.9 (10.9)	14.9 (12.4)	15.1 (12.6)	14.9 (12.2)*
	Emotional health	12.1 (7.6)	5.4 (7.5)	5.7 (7.4)	5.1 (6.9)**

*statistically significantly lower at P<0.05 (unadjusted comparison)
**statistically significantly lower at P<0.01 (unadjusted comparison)

Table 3.4 and Appendix Figure 3.3 show the MLHFQ scores over time by age group. One-way ANOVA tests showed statistically significantly higher (i.e., worse) scores for the youngest patients at all time points and on all subscales.

Table 3.4 MLHFQ scores over time by age group

		Mean score (SD) at time point			
		Baseline	**7 days**	**30 days**	**180 days**
MLHF total	**Age >79**	53.1 (23.6)	23.5 (24.8)	27.2 (24.1)	26.5 (24.8)
	Age 65-79	58.7 (25.5)	25.2 (23.8)	27.1 (24.3)	26.4 (23.5)
	Age 50-64	70.2 (25.9)*	35.3 (28.0)*	38.5 (29.9)*	36.8 (27.5)*
Physical health	**Age >79**	26.5 (10.2)	13.9 (11.9)	14.6 (11.9)	14.9 (12)
	Age 65-79	27.8 (11.0)	14.6 (12.5)	14.6 (12.4)	14.3 (12.3)
	Age 50-64	30.8 (10.4)*	17.4 (12.9)*	17.9 (13.2)*	18.0 (10.1)*
Emotional health	**Age >79**	10.4 (7.1)	4.3 (6.8)	5.0 (6.4)	5.3 (7.2)
	Age 65-79	12.1 (7.4)	5.0 (7.1)	5.3 (7.0)	4.8 (6.7)
	Age 50-64	14.3 (7.8)*	6.9 (8.0)*	7.6 (8.2)*	7.1 (7.8)*

**One-way ANOVA statistically significant at p<0.01*

Missing survey data analysis

See Appendix Table 3.5a-c for the frequency and percent missing for each time point in the survey (baseline, 7, 30 and 180 days). For the baseline survey 1310 patients (91%) completed all questions in the emotional health subscale, 1272 patients (88%) completed all questions in the physical health subscale and 1016 patients (71%) completed all questions in the remaining MLHFQ (“other” questions not pertaining to emotional nor physical health). Very few were missing all items at the baseline survey on those subscales; 36 (2%) were missing all 5 items on the emotional subscale, 32 (2%) were missing all 8 items on the physical subscale, and 28 (2%) were missing all items on the remaining 8 MLHF questions. By 180 days only 799 patients (56%) completed all items on the emotional health subscale, 760 (53%) completed all physical health items, and 684 (48%) completed all other items.

Bivariate statistics by missing group

Appendix Table 3.6 displays bivariate statistics by various missing categories (first two columns show differences between *partial/no* missing vs. *all* missing; last two columns show differences between *any* missing vs. *no* missing). Those with completely missing survey data were more likely to be in the oldest age group (>79 years old) compared to younger age groups. Forty-one percent of the oldest group were completely missing final survey data compared to 33% of 65-79 year olds and 27% of 50-64 year olds ($p<0.01$). Those with completely missing survey data were also more likely to have valvular disease, renal failure, and anemia. There was no statistically significant difference in the percent completely missing by gender, race/ethnicity, marital status, education, health literacy, income, mean social isolation score, social isolation status, or mean geriatric depression scale score. Among the 615 patients missing all survey data at 180 days, 217 (37%) were missing because they were known to be deceased before survey collection.

Examining those with no missing survey data compared to the group with any missing data, the bivariate results were similar to the above comparisons. Those with no missing data were statistically significantly more likely to be in the younger age groups (39% were 65-79, 32% were 50-64) compared to the oldest group (29% of patients older that 79 had no missing survey data; $p<0.05$ for all comparisons). There was no statistically significant difference by marital status, income, education, health literacy, social isolation, or mean social isolation score.

Given that mortality status is closely related to missingness in the questionnaire data (i.e., those individuals will not have MLHFQ data), I evaluated baseline difference in scores. Baseline emotional health scores did not differ by mortality status at 180 days. The mean baseline emotional health score in those alive throughout the study was 12.1 and the mean score for those who died during the study was 12.6 (t-test for the difference in means =-0.857, p=0.39). However, baseline physical health scores did differ: mean physical health scores were statistically significantly higher (indicating worse baseline physical health) for those who eventually died during the study [29.8 vs. 28.0, t=-2.13, p=0.03]. The overall MLHFQ score was also statistically significantly different by 180-day mortality status.

Regression models

See Table 3.7 for the mixed effects regression models (patient level random effects, hospital-level random effects and multiple imputation models). The table presents coefficients and 95 % confidence intervals for each model. Model 1 controls for treatment, time, the interaction of treatment and time, and patient-level random intercepts. In both treatment and usual care groups the coefficient for time at 7, 30 and 180 days is significant in the model, indicating that emotional health is significantly better at each post-baseline time point compared to baseline in-hospital emotional health [e.g., $\beta_{180days}$=-5.8, 95%CI(-6.6, -5.0)]. The coefficient for the interaction of treatment group and time at 180 days is also statistically significant [$\beta_{trt*180d}$=-1.1, 95%CI(-2.2, -0.02)], meaning that emotional health scores for those in the treatment group are 1.1 points below those in the usual care group on average, controlling for the effects of treatment and time and the random patient-level effects (random intercepts). The LR test for the model compared to a standard OLS model is statistically significant (X^2=511.7, p<0.0001).

Table 3.7 Mixed effects linear regression models for emotional health scores

	Model 1		**Model 2**		**Model 3**		**Model 4**	
Variable	Coef	95% CI	Coef	95% CI	Coef	95% CI	Coef	95% CI
Time								
7 days	-6.9	(-7.6, -6.1)	-7	(-7.9, -6.0)	-6.3	(-7.2, -5.5)	-4.6	(-5.6, -3.6)
30 days	-6.1	(-6.8, -5.4)	-6.3	(-7.5, -5.1)	-5.6	(-6.5, -4.7)	-3.5	(-4.5, -2.5)
180 days	-5.8	(-6.6, -5.0)	-6.2	(-7.7, -4.6)	-5	(5.9, -4.2)	-1.4	(-2.5, -0.4)
Treatment	-0.03	(-0.8, 0.8)	0.03	(-0.8, 0.8)	-0.1	(-0.9, 0.7)	0	(-1.0, 1.0)
Treatment by time								
Trt*7days	0.2	(-0.8, 1.2)	0.1	(-1.1, 1.3)	0	(-1.3, 1.3)	-0.5	(-1.9, 0.9)
trt*30 days	-0.3	(-1.3, 0.7)	-0.4	(-1.6, 0.8)	-0.2	(-1.5, 1.2)	-0.9	(-2.3, 0.5)
trt*180 days	-1.1	(-2.2, -0.02)	-1.3	(-2.6, -0.02)	-0.9	(-2.1, 0.4)	-1.7	(-3.2, -0.3)

Model 1: Mixed effects linear regression with patient-level random effects
Model 2: Mixed effects linear regression with hospital-level random effects
Model 3: Mixed effects linear regression after multiple imputation with EH outcome missing <3 items (hospital level random effects)
Model 4: Mixed effects linear regression after imputation of dead as worst HRQOL (hospital level random effects)

Model 2 controls for hospital-level random effects. The fixed effects portion of the model controlling for time, treatment and the interaction of the two (time*treatment) is similar to the patient-level random effects model. The coefficient for the interaction of treatment group at 180 days is -1.3 and is statistically significant [$\beta_{trt*180d}$=-1.3, 95%CI(-2.6, -0.02)]. The LR test for the random intercept model comparing it to standard OLS is statistically significant (X^2=71.2, p<0.0001). The LR test comparing the mixed effects model with both hospital-level random slopes and intercepts to the model for random intercepts only is statistically significant (X^2=10.61, P=0.001). By Cohen's rules of thumb, the effect size for the adjusted difference in mean emotional health scores is 0.17 (ES=adjusted difference in means/baseline SD in emotional health scores=1.3/7/6=0.17). This approaches a "small" difference, but is below the threshold.[126]

Model 3 imputes missing covariates and the emotional health outcome if the patient completed at least 2 out of the 5 emotional health items. In this model the effect of the intervention on emotional health at 180 days was similar in magnitude, but no longer statistically significant [$\beta_{trt*180d}$=-0.9, 95%CI(-2.1, 0.4)]. Finally, model 4 imputes the emotional health outcome as the worst possible score for those who died during the study. The coefficient for the effect of the treatment on emotional health at 180 days was similar in magnitude and statistically significant [$\beta_{trt*180d}$=-1.7, 95%CI(-3.2, -0.3)].

In the mixed models controlling for the interaction of social isolation, treatment and time, the interaction terms were not statistically significant (i.e., there was no differential effect of treatment on the socially isolated). This was consistent in patient-level random effects models as well as hospital-level random effects models. Table 3.8

in the Appendix shows the results of the model. In the mixed models controlling for the interaction of age group, treatment and time, the interaction terms were not statistically significant (i.e., there was no differential effect of treatment by age group). This was consistent in patient-level random effects models as well as hospital-level random effects models. Table 3.9 in the Appendix shows the results of the model. The multiple imputation models that evaluated the potential differential effect of treatment on emotional health by age and social isolation showed no statistically significant difference at 180 days.

Discussion

In the BEAT-HF trial both control and intervention groups showed improvements in emotional health from baseline, but there was a trivial statistically significant difference between the two groups at 180 days (i.e., better emotional health in the intervention group) both in bivariate analyses and in mixed effects modeling. There was no differential effect of treatment when looking at age subgroups or those who are socially isolated.

The improvement in HRQOL after hospitalization has been shown in prior studies.[155,166,167] Baseline scores in the BEAT-HF trial were worse than those in comparative studies looking at educational or telemonitoring interventions after hospital discharge. The improvement of approximately 20 points in the total MLHFQ score (Effect size=0.77) is similar to another study,[155] but more pronounced than a larger quasi-experimental study with multi-component interventions and intensities .[166] In addition to these longitudinal changes seen in all hospitalized patients with heart failure, the differences between treatment and control groups varies widely depending on the study population, the intervention and the time period. Changes in emotional health were similar to the BEAT-HF trial in one study,[155] but much larger in some other studies.[59,167,168]

The BEAT-HF population as a whole shows an improvement in MLHFQ total score that meets the generally accepted 5-point minimally important difference (MID),[59,60] but whether the difference in emotional health between the two groups at 180 days is *clinically significant* is unclear. A smaller quasi-experimental (non-randomized) study looking at the effects of remote monitoring on HRQOL in hospitalized CHF patients discovered an unadjusted 6-point difference on the emotional health subscale at 90 days between the intervention group and usual care group.[169] However, several differences are important to note: (1) unlike in other studies the usual care group in the small study did not improve post-hospitalization, (2) the differences were only adjusted for time, (3) this was a small study and (4) it was non-randomized. Thus comparing the effects of remote monitoring and/or nurse education on HRQOL between BEAT-HF trial and other smaller cohort or quasi-experimental studies is challenging.[155,166,167,169]

In this trial the standardized effect size for the mean difference in emotional health scores was 0.17, which approaches a “small” difference but is below the established threshold.[126] Importantly, no MID threshold has truly been established on the MLHFQ subscales, thus more research is needed to explore what may constitute a clinically minimally important difference in emotional health in heart failure patients. The 5 point MID on the total scale corresponds to an effect size of 0.2 (i.e., “small”), thus the adjusted difference on the emotional health scale in the BEAT-HF trial is similar to the standardized effect sizes in some of the initial studies by Rector and colleagues.[59,60]

The finding of no differential treatment effect on emotional health by age nor social isolation in the BEAT-HF study could be for several reasons: (1) the main effect of treatment on the general population is minimal and there is no power to detect a difference in smaller subgroups, (2) no such interaction effect exists, (3) the adherence to the intervention was poor in certain subgroups or (4) the emotional health measure itself (MLHFQ emotional subscale) is not nuanced enough to examine such an effect.

In general, as heart failure patients age they typically have increases in comorbidities, number of prescription medications, and level of frailty[67,81,156–159] In theory these factors may increase the need for—and receptivity to—increased disease management through monitoring or coaching.[160,161,170] However, as I discovered in the prior chapter's analysis on emotional health in older patients in the BEAT-HF trial they rate their physical health better than younger patients and may have increased coping skills despite more comorbidities (see Chapter 2, pgs. 45-46, and Appendix Table 2.5 for age differences in covariates in the BEAT-HF trial). [70,136,137] Thus, age differences in coping skills or acceptance of limitations may limit the effects of the intervention (or the ability to detect effects) on emotional health in these subgroups.

In terms of social isolation, only 20% of the BEAT-HF population classify as "isolated" at baseline, thus, after accounting for incomplete data, dropout and death over 180 days the sample size is likely too small to detect an effect (if one exists). It also may be that socially isolated individuals need more intensive interventions to see a change in emotional health.[163,166,171,172]

This study has several limitations. The use of a health-related quality of life survey opens up a potential for non-response bias (i.e. people who complete the survey are different from the people who don't) which could potentially alter the relationship between treatment group and emotional health. However, as Table 3.6 shows there are very few differences between those with *no* missing data and those with *some* missing data on survey items. In addition, I analyzed emotional health outcomes in those with complete data and then performed multiple imputation for those with missing survey items and found consistent effects of treatment on the outcome in mixed effects models (though, in the multiple imputation mixed effects model the 95% confidence interval for treatment effect crosses the line of unity).

With any telemonitoring intervention the diffusion and acceptability of that technology in the patient population of interest is important.[173] Given a wide variability of usage and compliance with the intervention (specifically, the telemonitoring equipment) it may be that the effects on emotional health were diminished because of non-compliance.[115] Other analyses assessing the effect of the intervention in those who were more compliant with the technology are ongoing. However, subgroup analyses will have limitations as there may be residual confounding based on differences in those who are more likely to use the equipment.

As noted, the emotional health measure in this study has additional limitations and likely does not completely encapsulate the complexity of the emotional health of heart failure patients or may not be as responsive to the intervention as other measures.[166]

Despite these limitations, the study is one of the largest randomized controlled trials analyzing remote monitoring and nurse education in a heart failure population, thus may be more representative of the real-world effects of the intervention in a broad heart failure population. In addition, I use an intent to treat analysis which may give a conservative estimate of the intervention's effect on emotional health. Within the statistical design, I attempt to control for the effects of correlated longitudinal data in addition to patient-level and hospital-level effects in the mixed effects design to account for these factors.

Conclusions

In the BEAT-HF trial there were large improvements in emotional health over time in both intervention and usual care arms. In addition, there was a small but statistically significant positive effect of the intervention on emotional health at 180 days. The adjusted difference in mean emotional health scores in the intervention group compared to the usual care group may be below the threshold for a minimally important difference. No differential treatment effect was found by age or social isolation status.

Conclusion to the dissertation

In this dissertation hypertension and heart failure were analyzed via different perspectives: hypertension through the population lens and heart failure through the patient's perspective and experience. Hypertension is an important upstream risk factor for coronary disease, stroke and heart failure, thus understanding mechanisms to improve hypertension control is key to reduce morbidity, mortality and costs.

In the first chapter of the dissertation I discovered that having access to a usual source of care is associated with a thirty percentage-point increase in the probability of hypertension control in the US population. This amounts to an additional 300,000 individuals with controlled hypertension per million in the US hypertensive population. The magnitude of effect has important implications for improving access to regular sources of care in the US, so that hypertension can be detected and appropriate behavioral and pharmaceutical interventions can be implemented to reduce the downstream complications of hypertension. In addition to the overall association between structural access to care and hypertension control, I discovered a differential association by age group. This difference was likely driven by behavioral factors in the youngest group and physiological factors in the oldest group. The varying impact of USOC on hypertension control across age groups may reflect a need to change strategies to control blood pressure in different age groups. Specifically, a focus on improving health behaviors in younger individuals may involve focusing on anti-hypertensive medication initiation and compliance, regular follow up, and cessation of smoking. Conversely, given that effect of having a USOC on blood pressure control is diminished in the oldest population, more information is needed to discover what strategies will most effectively improve health outcomes in the oldest and most vulnerable.

In chapters 2 and 3 of the dissertation, I explored patient-reported outcomes in a large heart failure population. In the BEAT-HF trial older age groups had better emotional health, as measured by the disease-specific MLHFQ. In addition, the association between age and emotional health was partially mediated by physical health. While the mediating role of physical health was anticipated, the improved emotional health and better self-reported physical health was unexpected. Interestingly, there was a higher proportion of nearly every major comorbidity in the oldest age group which would suggest potentially *more* physical limitations and frailty on average. In addition, the oldest age group also had diminished social networks, but despite these differences in comorbidities and isolation (and after controlling for these differences) older age was still associated with better emotional health. This may suggest an element of increased coping and acceptance of limitations in this older heart failure population.

In the final section, I reported a trivial but statistically significant effect of the intervention on emotional health in this population but no differential effect by age or social isolation. The adherence to the intervention in the BEAT-HF trial was limited, which may have minimized the true effect of the intervention on emotional health, but this large scale intent-to-treat analysis may be representative of the real-world effect of remote monitoring and nurse coaching on a broad population of heart failure patients.

The morbidity, mortality, direct and indirect costs of hypertension and heart failure are enormous. With the aging baby boomer population and high prevalence of risk factors—smoking, obesity, hyperlipidemia and hypertension—cardiovascular disease will remain one of the preeminent public health concerns in the future. Thus, the ongoing discovery and implementation of strategies to improve outcomes in hypertension and heart failure will be an ongoing challenge for the next generation of researchers and healthcare providers.

Appendix

Additional tables and figures for Chapter 2

Table 2.5 Characteristics of the Beat-HF population by age group

	Age 50-64 (n=416)	**Age 65-79** (n=507)	**Age>79** (n=513)	**Statistical significance**
Gender				
Female	158 (38%)	241 (47.5%)	265 (51.6%)	**
Race/ethnicity				
Hispanic	56 (13.4%)	72 (14.2%)	35 (6.9%)	**
Non-Hispanic Black	153 (36.7%)	113 (22.3%)	50 (9.9%)	**
Non-Hispanic White	162 (38.9%)	261 (51.5%)	356 (54.5%)	**
Other race	46 (11%)	61 (12%)	64 (12.7%)	
Marital status				
Married	152 (37.6%)	220 (44.2%)	213 (43.2%)	
Divorced	138 (34.2%)	125 (25.1%)	55 (11.2%)	**
Widowed	26 (6.4%)	96 (19.3%)	210 (42.6%)	**
Never married	88 (21.8%)	57 (11.45%)	160 (11.5%)	**
Education				
Less than high school	54 (13.4%)	91 (18.4%)	67 (15.2%)	
High school graduate	241 (59.7%)	233 (47%)	254 (51.5%)	**
College graduate	109 (27%)	172 (34.7%)	172 (34.9%)	*
Health literacy				
At risk for poor health literacy (no. and % with REALM-R<7)	128 (31.1%)	153 (30.4%)	147 (29.3%)	
Annual household family income				
<$25 K	167 (51.5%)	162 (40%)	114 (30%)	**
$25-50K	83 (25.6%)	101 (24.9%)	101 (26.6%)	
$50-75K	30 (9.3%)	58 (14.3%)	75 (19.7%)	**
>$75K	44 (13.6%)	84 (20.7%)	90 (23.7%)	**
Social isolation				
Lubben social network Scale score (mean, SD)	17.6 (7.0)	18.1 (6.9)	16.0 (6.0)	**
"Isolated" (no. and % with LSNS<12)	89 (22.3%)	89 (18.1%)	114 (23.7%)	
MLHFQ , *mean(SD)*				
Combined score (0-105)	70.2 (25.9)	58.7 (25.5)	53.1 (23.6)	**
Physical health score (0-40)	30.8 (10.4)	27.8 (11.0)	26.5 (10.2)	**
Emotional health score (0-25)	14.3 (7.8)	12.1 (7.4)	10.4 (7.1)	**
"Other" health score (0-40)	25.1 (10.2)	19.5 (10.0)	15.7 (8.9)	**
NHYA class				

Class I-II	79 (25.9%)	115 (28.5%)	100 (21.5%)	
Class III	185 (60.7%)	248 (61.4%)	327 (70.3%)	**
Class IV	41 (13.4%)	41 (10.2%)	38 (8.2%)	
Medical comorbidities				
Valvular heart disease	11 (2.7%)	37 (7.6%)	46 (9.5%)	**
Peripheral Vascular disease	26 (6.5%)	59 (12.1%)	82 (17.0%)	**
Hypertension	278 (69.0%)	327 (67.3%)	335 (69.4%)	
Diabetes mellitus	214 (53.1%)	243 (50.0%)	170 (35.2%)	**
Renal failure	134 (33.3%)	198 (40.7%)	207 (42.9%)	**
Rheumatoid Arthritis or Collagen Vascular disease	11 (2.7%)	25 (5.1%)	14 (2.9%)	
COPD	121 (30.0%)	153 (31.5%)	134 (27.7%)	
Hypothyroid	56 (13.9%)	102 (21.0%)	124 (25.7%)	**
Obesity	95 (23.6%)	93 (19.1%)	40 (8.3%)	**
Anemia	89 (22.1%)	163 (33.5%)	197 (40.8%)	**
Substance abuse	63 (15.6%)	13 (2.7%)	7 (1.5%)	**
Geriatric Depression Scale				
Total score (mean, SD)	4.9 (3.6)	4.3 (3.0)	3.9 (2.7)	**
No depression	233 (57.3%)	317 (63.7%)	328 (66.4%)	*
Mild depression	102 (25.1%)	127 (25.5%)	132 (26.7%)	
Moderate depression	45 (11.1%)	44 (8.8%)	30 (6.1%)	*
Severe depression	27 (6.6%)	10 (2.0%)	4 (2.9%)	**

**Significant at P<0.05*

***Significant at P<0.01*

Table 2.7 Missing data for the BEAT-HF trial

Variable	No. Missing	Total	Percent missing
Age	8	1437	0.60%
Gender	0	1437	0
Education	44	1437	3%
Race/ethnicity	8	1437	0.60%
Marital status	42	1437	2.90%
Income	328	1437	22.80%
Valvular disease	65	1437	4.50%
Vascular disease	65	1437	4.50%
COPD	65	1437	4.50%
Diabetes	65	1437	4.50%
Hypertension	65	1437	4.50%

Renal disease	65	1437	4.50%
Hypothyroid	65	1437	4.50%
Rheumatoid arth/Collagen vasc.	65	1437	4.50%
Substance abuse (ETOH or drugs)	65	1437	4.50%
NYHA class	263	1437	18.30%
LSNS total score	63	1437	4.40%
LSNS isolated	63	1437	4.40%
Geriatric Depression Scale Total	38	1437	2.60%
Baseline MLHFQ items			
Burden	85	1437	5.90%
Self control	65	1437	4.50%
Worry	50	1437	3.50%
Concentration	53	1437	3.70%
Depressed	62	1437	4.30%
Emotional subscale	127	1437	8.80%
Sit	49	1437	3.40%
Stairs	73	1437	5.10%
Yard work	75	1437	5.20%
Going places	52	1437	3.60%
Sleeping	54	1437	3.80%
Recreation	67	1437	4.70%
Shortness of breath	53	1437	3.70%
Fatigue	50	1437	3.50%
Physical subscale	165	1437	11.50%
Friends/family	61	1437	4.20%
Side effects	104	1437	7.20%
Cost money	82	1437	5.70%
Hospital	59	1437	4.10%
Food	60	1437	4.20%
Earn Living	166	1437	11.60%
Sex	266	1437	18.50%
Swelling	59	1437	4.10%
Other subscale	421	1437	29.30%

Table 2.10 Quantile Regression coefficients and 95% CIs for emotional health scores

Variable	Quantile regression at 0.25 quantile	Quantile regression at 0.50 quantile	Quantile regression at 0.75 quantile
Age strata			
Age >79	-2.2	-2.1	-2.7
	(-3.9, -0.4)	(-3.2, -1.0)	(-3.7, -1.7)
Age 65-79	-1.5	-1.2	-1.6
	(-3.1, 0.2)	(-2.3, -0.2)	(-2.5, -0.7)
Social Isolation			
"Isolated" (LSNS<12)	-0.8	0.4	0.2
	(-2.4, 0.9)	(-0.6, 1.5)	(-0.7, 1.2)
Physical Health (PH score on MLHFQ)	0.4	0.4	0.5
	(0.33,0.44)	(0.4,0.48)	(0.4, 0.51)
Medical comorbidities			
Hypothyroid	0.3	1	0.4
	(-1.3, 1.9)	(-0.04, 2.0)	(-0.5, 1.3)
Substance abuse	1.5	0.8	0.4
	(-1.3, 4.4)	(-1.1, 2.6)	(-1.2, 2.1)
Anemia	0.8	0.4	0.4
	(-0.6, 2.1)	(-0.4,1.3)	(-0.3, 1.2)
Obesity	-1.2	-0.2	0.2
	(-3.9, 0.7)	(-1.3, 0.9)	(-0.8, 1.2)

Table 2.13 Mixed effects linear regression with hospital level random effects for emotional health scores

Variable	Coeff	95% CI
Age strata		
Age >79	-1.3	(-1.9, -0.6)
Age 65-79	-1	(-1.5 ,-0.4)
Female	0.1	(-0.4, 0.5)
Race/Ethnicity		
Hispanic	0.7	(-0.01, 1.4
Non Hispanic Black	-0.1	(-0.7, 0.5)
Other race	-0.3	(-1.0, 0.3)
Marital status		
Married	0.04	(-0.5, 0.6)
Never Married	-0.3	(-1.0, 0.5)

Widowed	-0.2	(-0.9, 0.4)
Health literacy		
At risk for poor health literacy (REALM-R<7)	0.02	(-0.5, 0.7)
Annual household family income		
$25-50K	-0.2	(-0.7, 0.4)
$50-75K	-0.1	(-0.8, 0.6)
>$75K	-0.1	(-0.7, 0.5)
Social Isolation		
"Isolated" (LSNS<12)	0.6	(0.1, 1.1)
Physical Health (PH score on MLHFQ)	0.4	(0.39, 0.43)
Medical comorbidities		
Valvular disease	0.1	(-0.8, 1.0)
Vascular disease	0.4	(-0.3, 1.0)
COPD	-0.1	(-0.6, 0.3)
Diabetes	0.2	(-0.3, 0.6)
End stage kidney disease	-0.6	(-1.1,- 0.2)
Hypertension	-0.2	(-0.7, 0.2)
Hypothyroid	0.6	(0.1, 1.1)
Rheumatoid arthritis	-1.1	(-2.2, 0.03)
Obesity	-0.2	(-0.8, 0.3)
Anemia	0.6	(0.1, 1.0)
Substance abuse	0.4	(-0.5, 1.3)
Time	-0.5	(-0.7, -0.3)

*LR test for model with hospital-level random intercepts is significant (X^2=6.84, P=0.0045)

Figure 2.3 Univariate distributions of variables in the BEAT-HF population

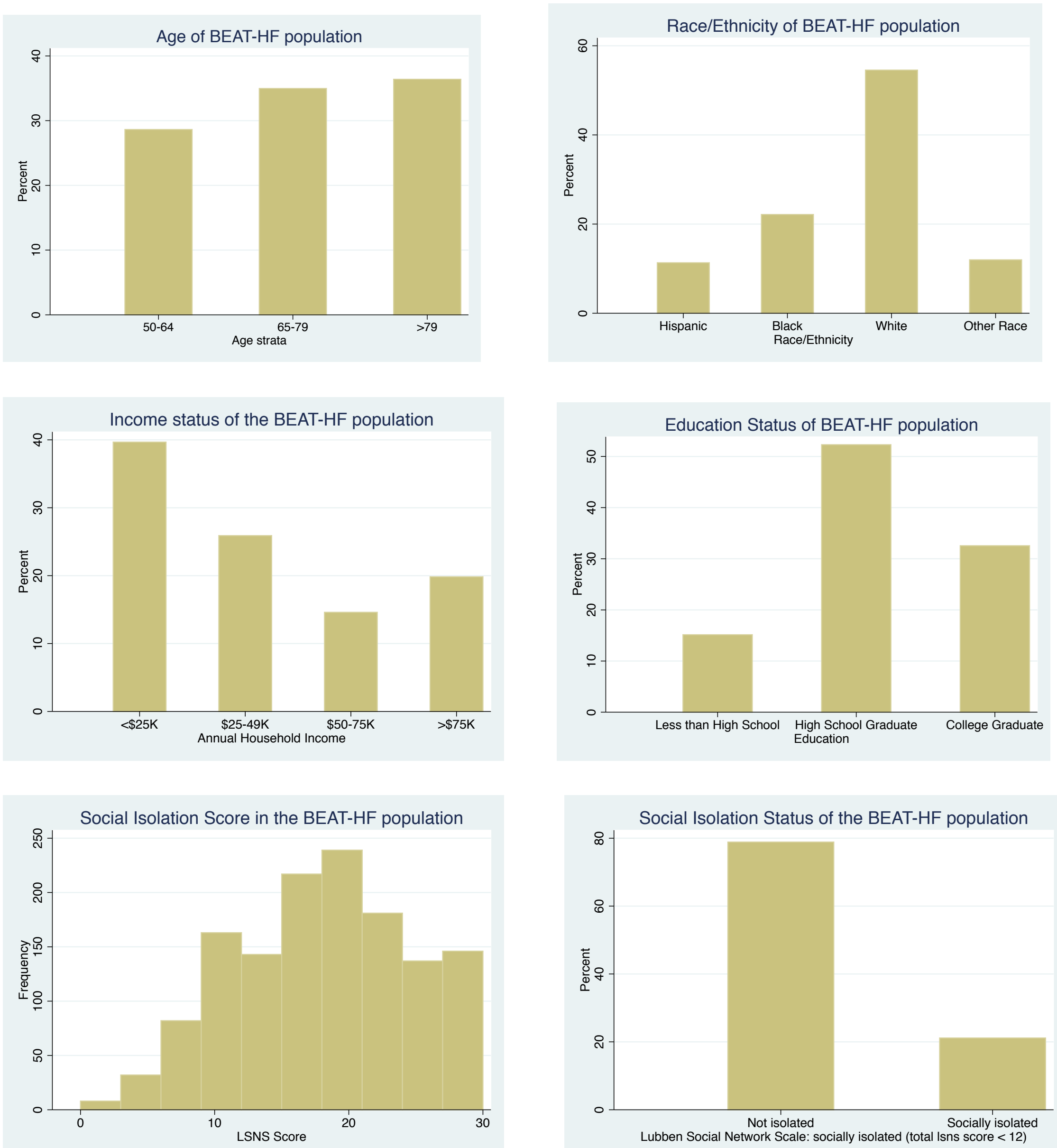


Figure 2.3 (cont.) Univariate distributions of variables in the BEAT-HF population

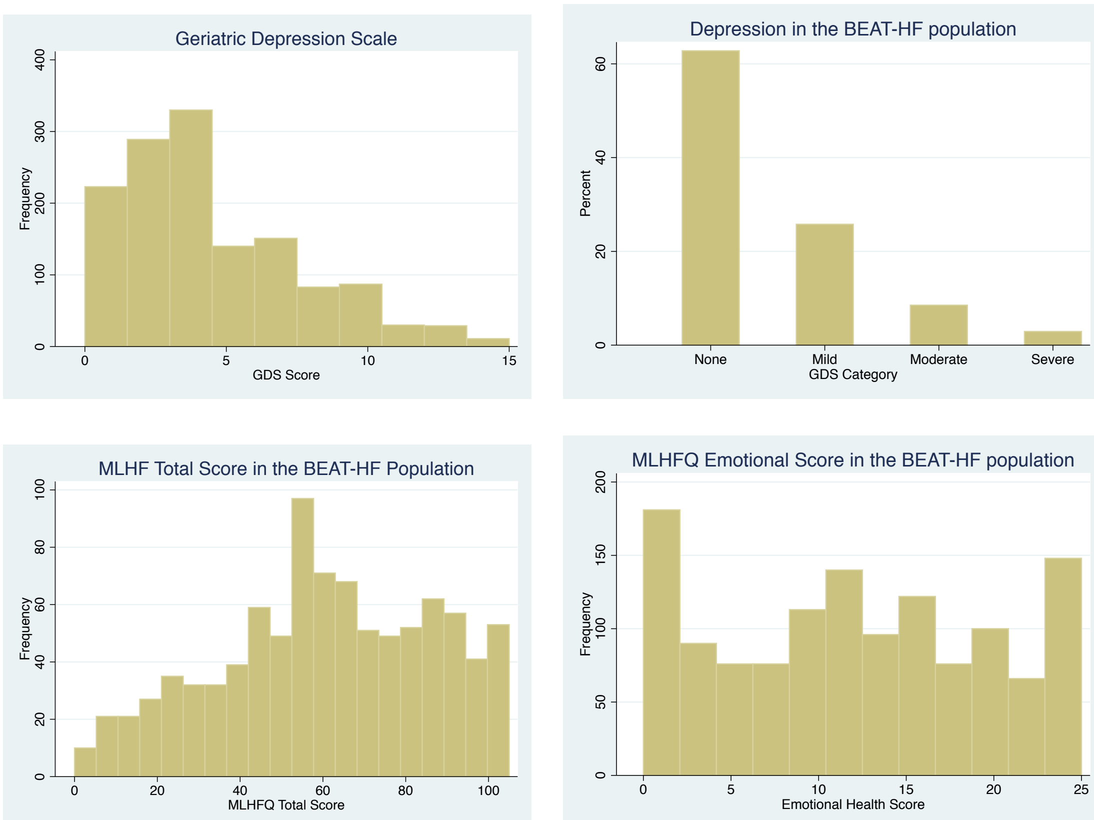


Figure 2.4b Boxplot graphs: bivariate associations with Emotional Health

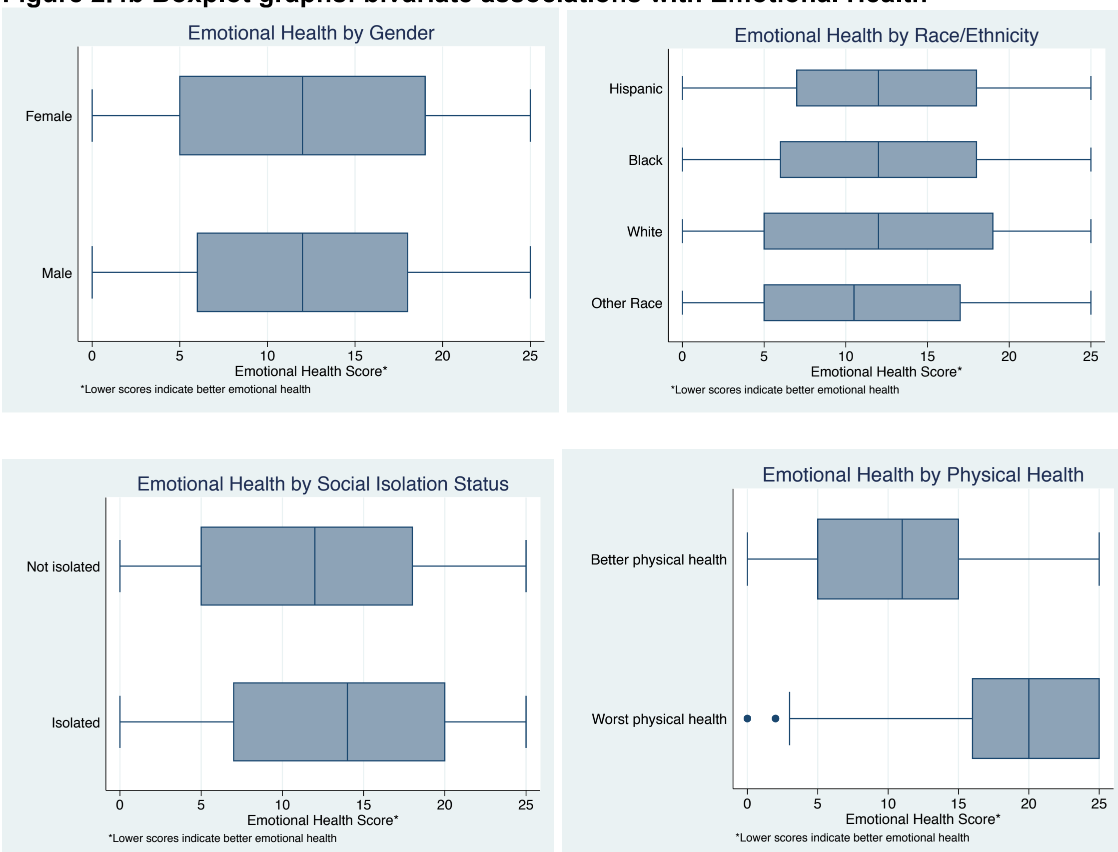
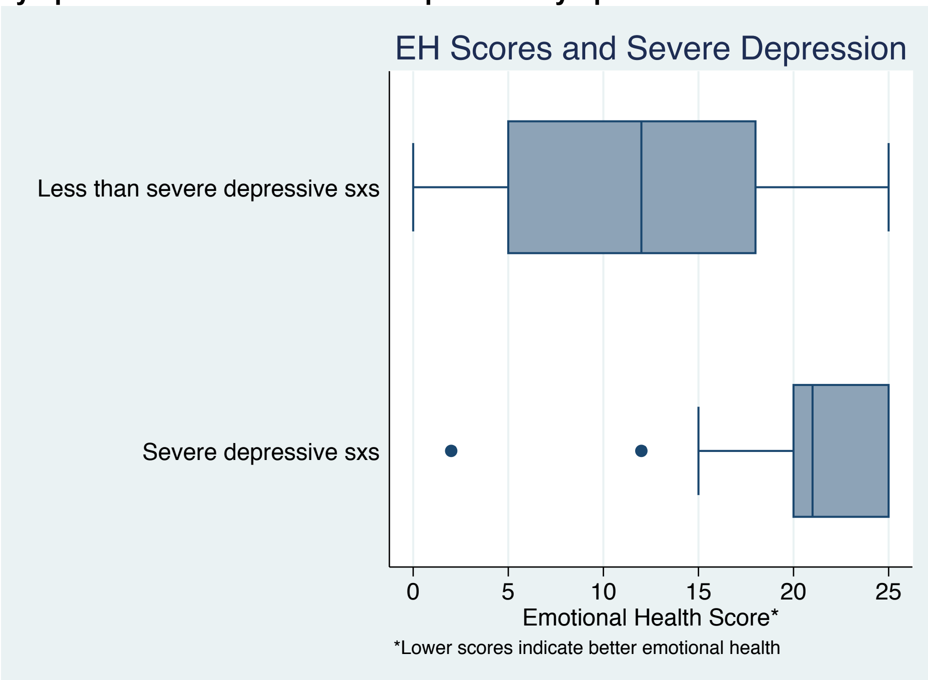


Figure 2.5 Distribution of Emotional Health Scores by Depression Group: *severe* depressive symptoms vs *less than severe* depressive symptoms #



#Cohen's d coefficient=-1.18 (bootstrapped 95% CI (-1.52, -0.84)) for the difference in EH mean scores in Severe Depression vs. Less than severe depression.

Figure 2.6 Quantile regression coefficient graphs for emotional health scores

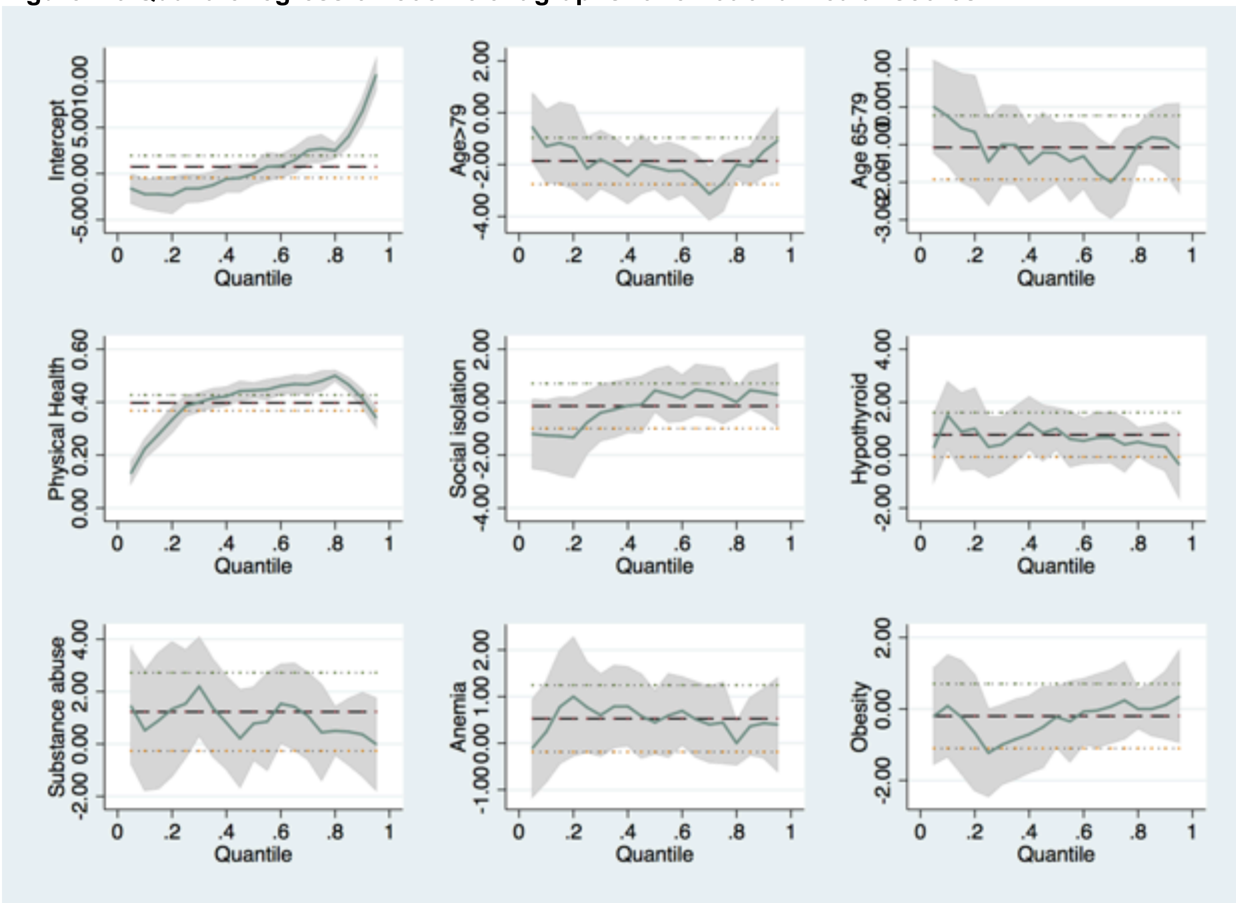


Figure 2.7 Legend:
Green line- Regression coefficient in quantile regression
Shaded gray area—95% confidence intervals for quantile regression coefficient
***Black solid hash line** —OLS coefficient*
Orange and green small dotted line—95% confidence interval for OLS coefficient

Additional tables and figures for Chapter 3

Table 3.5a Missing emotional health survey data across time points

	Baseline survey		7 days		30 days		180 days	
Number missing	Frequency	%	Frequency	%	Frequency	%	Frequency	%
0	1310	91.20%	1013	70.50%	991	69.00%	799	55.60%
1	64	4.50%	23	1.60%	14	1.00%	12	0.80%
2	17	1.20%	1	0.10%	3	0.20%	4	0.30%
3	3	0.20%	1	0.10%	1	0.10%	4	0.30%
4	7	0.50%	0	0.00%	1	0.10%	0	0%
5	36	2.50%	399	27.80%	427	29.70%	618	43%
Total	**1437**	**100%**	**1437**	**100%**	**1437**	**100%**	**1437**	**100%**

Table 3.5b Missing physical health survey data across time points

	Baseline survey		7 days		30 days		180 days	
Number missing	Frequency	%	Frequency	%	Frequency	%	Frequency	%
0	1272	88.50%	944	65.70%	939	65.30%	760	52.90%
1	91	6.30%	64	4.50%	53	3.70%	40	2.80%
2	20	1.40%	26	1.80%	14	1%	15	1%
3	12	0.80%	6	0.40%	6	0.40%	5	0.40%
4	3	0.20%	2	0.10%	1	0.10%	1	0.10%
5	5	0.40%	2	0.10%	0	0.00%	0	0.00%
6	1	0.10%	2	0.10%	1	0.10%	0	0.00%
7	1	0.10%	1	0.10%	0	0.00%	1	0.10%
8	32	2.20%	390	27.10%	423	39.40%	615	42.80%
Total	**1437**	**100%**	**1437**	**100%**	**1437**	**100%**	**1437**	**100%**

Table 3.5c Missing "other" health survey data across time points

	Baseline survey		7 days		30 days		180 days	
Number missing	Frequency	%	Frequency	%	Frequency	%	Frequency	%
0	1016	70.70%	888	61.80%	855	59.50%	684	47.60%
1	238	16.60%	108	7.50%	114	7.90%	96	6.70%
2	111	7.70%	36	2.50%	31	2.20%	30	2.10%
3	27	1.90%	5	0.40%	12	0.80%	7	0.50%
4	6	0.40%	3	0.20%	1	0.10%	3	0.20%
5	3	0.20%	0	0.00%	0	0%	0	0.00%
6	3	0.20%	1	0.10%	0	0%	1	0.10%
7	5	0.40%	3	0.20%	4	0.30%	1	0.10%
8	28	2.00%	393	27.40%	420	29.20%	615	42.80%
Total	**1437**	**100%**	**1437**	**100%**	**1437**	**100%**	**1437**	**100%**

Table 3.6 Bivariate statistics by missing data group (missing survey data at 180 days)

Variable	Partial or no missing (n=822)	Missing all survey data (n=615)		Any missing (n=775)	No missing (n=662)	
Age						
>79	263 (32%)	250 (40.7%)	**	322 (41.6%)	191 (28.9%)	**
65-79	306 (37.2%)	201 (32.7%)		249 (32.1%)	258 (39%)	**
50-64	253 (30.8%)	164 (26.7%)		204 (26.3%)	213 (32.2%)	*
Gender						
Female	395 (48%)	269 (43.8%)		355 (45.9%)	309 (46.7%)	
Race/ethnicity						
Hispanic	102 (12.4%)	61 (10%)		66 (8.6%)	97 (14.7%)	**
Non-Hispanic Black	186 (22.7%)	130 (21.4%)		165 (21.5%)	151 (22.8%)	
Non-Hispanic White	437 (53.2%)	342 (56.3%)		438 (57%)	341 (51.6%)	*
Other race	96 (11.7%)	75 (12.3%)		99 (12.9%)	72 (10.9%)	
Marital status						
Married	340 (42.2%)	245 (41.6%)		302 (40.4%)	283 (43.7%)	
Divorced	188 (23.3%)	130 (22.1%)		161 (21.6%)	157 (24.2%)	
Widowed	181 (22.5%)	151 (25.6%)		203 (27.2%)	129 (19.9%)	
Never married	97 (12%)	63 (10.7%)		81 (10.8%)	79 (12.2%)	
Education						
Less than high school	125 (15.5%)	87 (14.8%)		105 (14.1%)	107 (16.5%)	
High school graduate	423 (52.5%)	305 (52%)		397 (53.4%)	331 (51%)	
College graduate	258 (32%)	195 (33.2%)		242 (32.5%)	211 (32.5%)	
Health literacy						
At risk for poor health literacy	237 (29%)	191 (31.9%)		244 (32.2%)	184 (28%)	
Annual household family income						
<$25 K	268 (40.5%)	175 (39.1%)		217 (37.4%)	226 (42.8%)	
$25-50K	167 (25.3%)	118 (26.3%)		162 (27.9%)	123 (23.3%)	
$50-75K	96 (14.5%)	67 (15%)		86 (14.8%)	77 (14.6%)	
>$75K	130 (19.7%)	88 (19.6%)		116 (20%)	102 (19.3%)	
Social isolation						
LSNS score (mean, SD)	17.4 (6.7)	17 (6.6)		17 (6.5)	17.5 (6.8)	
"Isolated" (no. and % with LSNS<12)	166 (20.7%)	126 (22%)		157 (21.5%)	135 (21%)	
NHYA class						
Class I-II	156 (23.9%)	138 (26.4%)		155 (23.7%)	139 (26.7%)	
Class III	422 (64.7%)	338 (64.8%)		437 (66.9%)	323 (62%)	
Class IV	74 (11.4%)	46 (8.8%)		61 (9.3%)	59 (11.3%)	
Medical comorbidities						

Valvular heart disease	44 (5.5%)	50 (8.7%)	*	60 (8.2%)	34 (5.3%)	*
Peripheral Vascular disease	88 (11%)	79 (13.7%)		96 (13.2%)	71 (11.1%)	
Hypertension	562 (70.5%)	378 (65.7%)		487 (66.7%)	453 (70.6%)	
Diabetes mellitus	370 (46.4%)	257 (44.7%)		330 (45.2%)	297 (46.3%)	
Renal failure	285 (35.8%)	254 (44.2%)	**	307 (42.1%)	232 (36.1%)	*
RA or Collagen Vascular disease	28 (3.5%)	22 (3.8%)		26 (3.6%)	24 (3.7%)	
COPD	243 (30.5%)	165 (28.7%)		217 (29.7%)	191 (29.8%)	
Hypothyroid	161 (20.2%)	121 (21%)		149 (20.4%)	133 (20.7%)	
Obesity	145 (18.2%)	83 (14.4%)		112 (15.3%)	116 (18.1%)	
Anemia	236 (29.6%)	213 (37%)	**	267 (36.6%)	182 (28.4%)	**
Substance abuse	47 (5.9%)	36 (6.3%)		46 (6.3%)	37 (5.8%)	
Geriatric Depression Scale						
Total score (mean, SD)	4.2 (3.1)	4.5 (3.1)		4.4 (3.1)	4.3 (3.2)	
No depression	528 (65.2%)	350 (59.4%)	*	462 (61.7%)	416 (64%)	
Mild depression	193 (23.8%)	168 (28.5%)	*	200 (26.7%)	161 (24.8%)	
Moderate depression	63 (7.8%)	56 (9.5%)		67 (9%)	52 (8%)	
Severe depression	26 (3.2%)	15 (2.6%)		20 (2.7%)	21 (3.2%)	

*Significant at P<0.05
**Significant at P<0.01

Table 3.8 Mixed effects linear regression for emotional health scores (interaction of treatment with social isolation)

Variable	Coefficient	95% CI
Time		
7 days	-6.7	(-7.6, -5.7)\
30 days	-6.3	(-7.3, -5.3)
180 days	-6.1	(-7.1, -5.0)
Treatment	0.3	(-0.6, 1.2)
Treatment by time		
Trt*7days	-0.4	(-1.8, 0.9)
trt*30 days	-0.3	(-1.6, 1.1)
trt*180 days	-1.1	(-2.5, 0.4)
Social isolation by time		
Isol*7 days	-1.2	(-3.0, 0.6)
Isol*30 days	0.6	(-1.7, 1.9)
Isol*180 days	0.8	(-1.4, 2.5)
Time*Trt*Social isolation		
Isol*Trt*7	2.7	(0.2, 5.3)
Isol*Trt*30	0.4	(-2.2, 2.9)

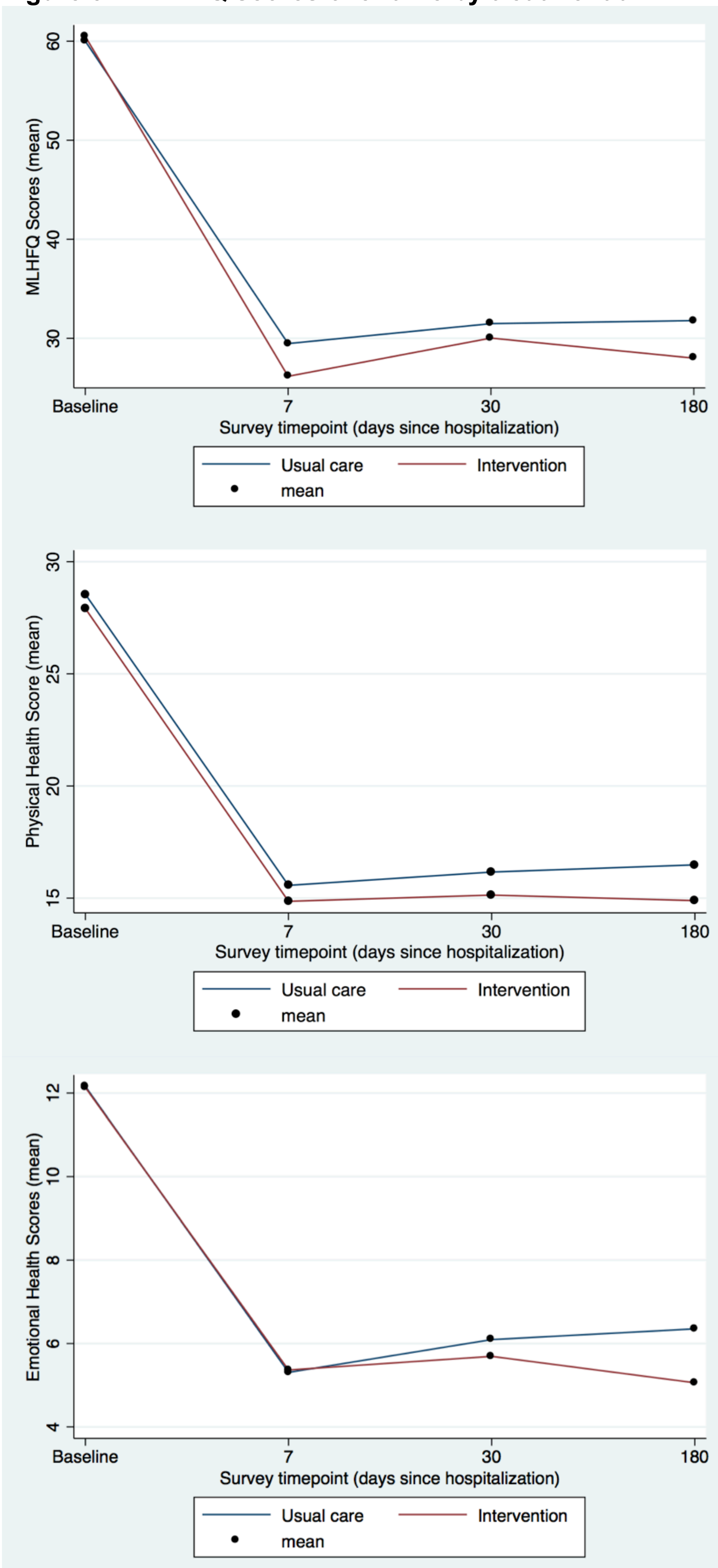
Isol*Trt*180	-0.5	(-3.3, 2.2)

Table 3.9 Mixed effects linear regression for emotional health scores (interaction of treatment with age) *

Variable	Coefficient	95% CI
Time		
7 days	-6.7	(-8, -5.4)
30 days	-6	(-7.3, -4.6)
180 days	-6	(-7.4,-4.6)
Treatment	0.1	(-1.3, 1.6)
Age		
Age 65-74	-2.3	(-3.7, -1)
Age >74	-3.3	(-4.8, -1.9)
Time*Trt*Age		
7 days*trt*age 65-74	2.5	(-0.5, 5.4
7 days*trt*age>74	1.8	(-1.2, 4.8)
30 days*trt*age 65-74	1.5	(-1.4, 4.5)
30 days*trt*age>74	2,2	(-0.8, 5.2)
180 days*trt*age 65-74	0.1	(-3, 3.2)
180 days*trt*age>74	3.2	(-0.1, 6.4)

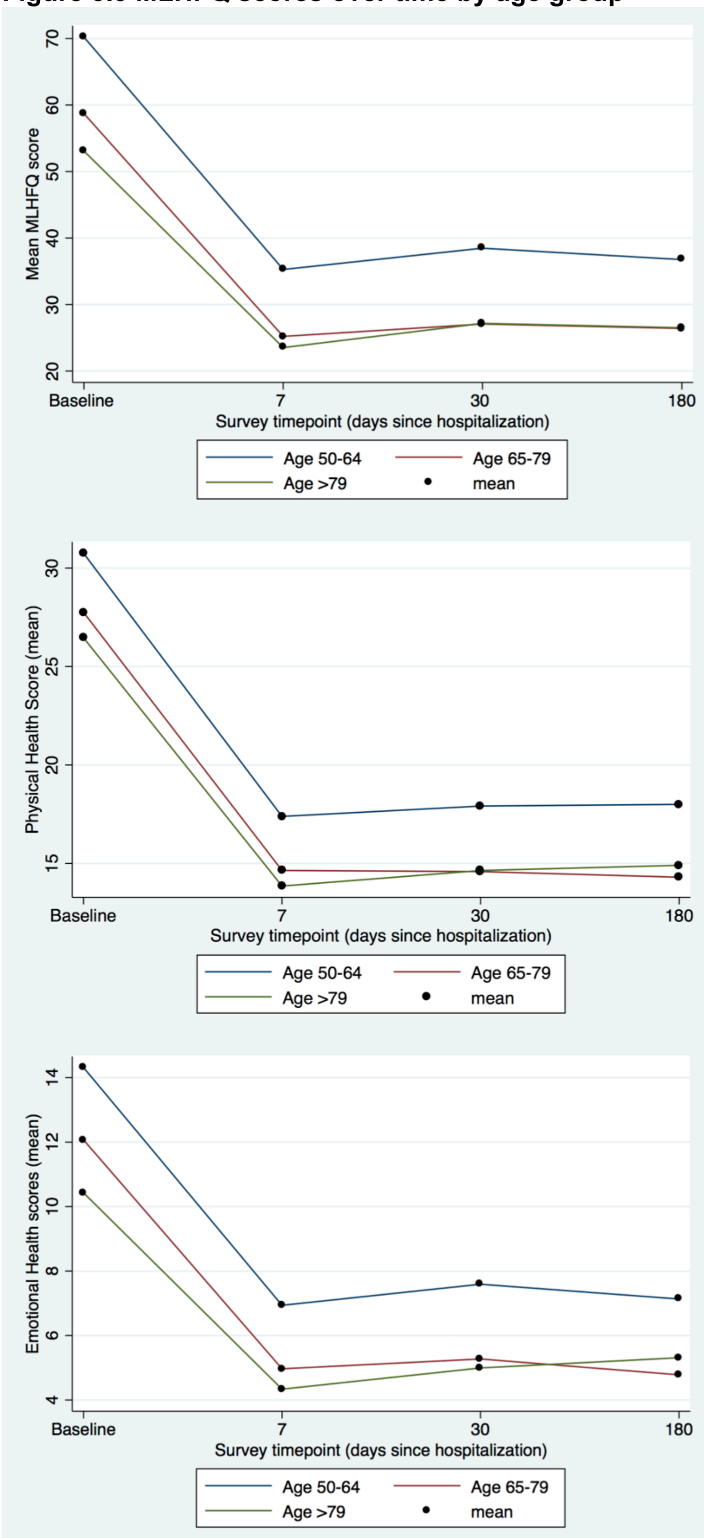
*Not all interactions shown in table. Coefficients for Time*trt, time*age and trt*age left out for simplicity

Figure 3.2 MLHFQ scores over time by treatment arm*



*unadjusted comparison of scores between treatment groups significantly different at 180 days (P<0.05 for MLHFQ summary and Physical subscales, P<0.01 for Emotional subscale)

Figure 3.3 MLHFQ scores over time by age group*



*One-way ANOVA for difference in mean scores across age groups statistically significantly different at all time-points and on all scales

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