SOCIOECONOMIC STATUS AND THE PROGRESSION OF HEART FAILURE

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ABSTRACT

Socioeconomic Status and the Progression of Heart Failure

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(Under the direction of Wayne D. Rosamond)

This dissertation explores the relationship between socioeconomic status and the progression of heart failure following an incident heart failure hospitalization, defined in three domains: rehospitalization, mortality and self-rated health. Hospital admissions for heart failure are on the rise in the United States, and mortality remains high among heart failure patients. Meanwhile, self-rated health is a potent predictor of future health, and its trajectory among heart failure patients is unknown.

The first aim was to estimate the effect of neighborhood socioeconomic and Medicaid status on the time to first rehospitalization and the rehospitalization rate. Participants who lived in low neighborhood socioeconomic areas at baseline who had multiple comorbidities during the incident heart failure hospitalization were rehospitalized faster and more often compared to participants living in high socioeconomic neighborhoods at baseline with multiple comorbidities. Meanwhile, Medicaid recipients with a low level of comorbidity were rehospitalized faster and more often compared to non-Medicaid recipients.

The second aim was to estimate the effect of neighborhood socioeconomic and Medicaid status on the time to and risk of mortality. Participants who lived in low neighborhood

socioeconomic areas at baseline who had multiple comorbidities during the index heartfailure hospitalization experienced a shorter time to death compared to participants living in high socioeconomic neighborhoods at baseline with multiple comorbidities.

A comparison of the trajectory of self-rated health across time was examined among participants as part of the third aim. Predictors of a decline in self-rated health across time were assessed, and factors shown to contribute to poorer self-rated health regardless of incident disease status included advanced age, low educational attainment, current smoking and obesity.

This dissertation brings to attention several areas for future research in cardiovascular disease epidemiology. The first is a need to better understand the relationship of socioeconomic status and the progression of heart failure in terms of its out-of-hospital management. The second is to explore the mechanisms underlying the relationship between poor socioeconomic status and increased mortality. Lastly, interventions can be tested to help understand how to improve self-rated health, and the resulting health outcomes, among aging adults.

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LIST OF ABBREVIATIONS

ACC	American College of Cardiology
ADHERE	Acute Decompensated HEart failure national REgistry
AHA	American Heart Association
ANOVA	analysis of variance
ARIC	Atherosclerosis Risk in Communities study
BMI	body mass index
CHD	coronary heart disease
CVD	cardiovascular disease
DAG	directed acyclic graph
GFR	glomerular filtration rate
HF	heart failure
HR	hazard ratio
IHD	ischemic heart disease
MD	Maryland
MN	Minnesota
MS	Mississippi
NC	North Carolina
OR	odds ratio
RR	rate ratio
SES	socioeconomic status
SRH	self-rated health
US	United States
95% CI	95% confidence interval

I. INTRODUCTION

The public health burden of heart failure (HF) is rising. Hospital discharges for HF increased 157% from 1979 to 2002 (*Heart Disease and Stroke Statistics - 2005 Update*, 2005), and continue to rise (D. Lloyd-Jones et al., 2010). HF rehospitalizations, which are often preventable (MedPAC, 2007), tend to be higher among older patients, non-whites, and patients with prior hospitalizations and multiple primary care visits (Fang, Mensah, Croft, & Keenan, 2008; Ghali, Cooper, & Ford, 1990; Inouye et al., 2008; Schocken et al., 2008). In addition to being recognized as a major cause of serious morbidity (Adams et al., 2005; Cowie et al., 2002; H. Eriksson, 1995; Hoyt & Bowling, 2001), HF mortality is high (Jong, Vowinckel, Liu, Gong, & Tu, 2002; M. S. Nieminen & Harjola, 2005). From 1980 to 1995, the number of deaths in the US with an underlying cause of HF increased nearly 70% (Haldeman, Croft, Giles, & Rashidee, 1999). It is estimated that HF is a primary or contributory cause of more than 300,000 deaths each year in the US (Hunt et al., 2001), and HF mortality rates increase sharply with age. In addition, while HF survival has been shown to be worse than other cardiovascular diseases and cancers, with the exception of lung cancer (Simon Stewart, MacIntyre, Hole, Capewell, & McMurray, 2001), it remains unknown if trajectories in self-rated health (SRH) among HF patients show similar trends.

In this work, we characterized the relationship between neighborhood socioeconomic status (SES) and HF progression among ARIC cohort participants. Risk factors for HF and comorbid conditions tend to be more common among patients of low SES (Kaplan & Keil,

1993; McAlister, Stewart, Ferrua, & McMurray, 2004). Low individual SES, measured by factors such as income, education and occupation, implies limited economic resources available to the individual. While low neighborhood SES and individual SES are shown to have a negative effect on health outcomes (CDC, 2005; Chaix, Rosvall, & Merlo, 2007; Stjarne, Fritzell, Ponce de Leon, & Hallqvist, 2006; Suadicani, Hein, & Gyntelberg, 2001), their individual and joint effects on HF progression are not yet established. Meanwhile, health insurance status may be associated with care-seeking behavior (Philbin & DiSalvo, 1999) and subsequent disease outcomes (Ayanian, Kohler, Abe, & Epstein, 1993). Medicaid, in particular, may exert effects on health outcomes which are independent of SES (Foraker et al., 2008; Ross & Mirowsky, 2000), as its receipt is determined by having certain diseases and disabilities or an income below the poverty line (Ku, 2005; Rosenbaum, 2002).

Possible pathways linking lower neighborhood socioeconomic and Medicaid status to faster and more deleterious HF progression may include limited access to primary care, and inadequate management of HF symptoms out-of-hospital. However, we further speculated that it was possible for low neighborhood SES to impart a larger influence, for example, among participants with a higher burden of comorbidity, resulting in a shorter time to readmission, higher mortality and a steeper decline in SRH among these HF patients.

To the extent these findings are generalizable, they may lead to more effective management of HF patients, decreasing the burden of HF progression among patients with higher levels of comorbidity. For example, in the event neighborhood SES operates via comorbid disease to further contribute to the progression of HF, interventions (O'Dwyer, Baum, Kavanagh, & Macdougall, 2007) could be targeted to address the needs of patients of low neighborhood SES who also have high comorbidity.

This dissertation explored three aspects of the public health burden of incident HF. First, we examined neighborhood socioeconomic and Medicaid status and their association with rehospitalization among patients with incident hospitalized HF. Second, we explored the association of neighborhood socioeconomic and Medicaid status with mortality among patients with incident hospitalized HF. Lastly, we captured the effect of neighborhood SES on the trajectory of SRH among participants with incident HF, and compared the trajectory to that of participants with other types of incident disease.

II. SPECIFIC AIMS

Aim 1: Estimate the effect of neighborhood socioeconomic and Medicaid status on rehospitalization among patients with an incident HF hospitalization.

Aim 1a: Determine whether the relationship is modified by the presence or absence of chronic conditions or by age, race/study community, gender or individual SES.

We hypothesize that patients of lower neighborhood SES will have shorter times to readmission and more frequent hospitalizations, as will Medicaid recipients. It is possible that both low neighborhood SES and receipt of Medicaid impart a larger influence among patients with a higher burden of comorbidity, resulting in a shorter time to rehospitalization and more frequent readmissions.

Aim 2: Estimate the effect of neighborhood socioeconomic and Medicaid status on mortality among patients with an incident HF hospitalization.

Aim 2a: Determine whether the relationship is modified by the presence or absence of chronic conditions or by age, race/study community, gender or individual SES.

We hypothesize that patients of lower neighborhood SES will have shorter times to death following an incident HF hospitalization, as will Medicaid recipients. It is possible that both

low neighborhood SES and receipt of Medicaid impart a larger influence among patients with a higher burden of comorbidity, resulting in a shorter time to death among these patients.

Aim 3: Describe and compare the trajectory of self-rated health among participants with different disease states, such as those who remain disease-free throughout follow-up and those who experience incident HF, myocardial infarction, stroke, lung cancer, or receive a cardiac procedure.

Aim 3a: Describe and compare the trajectory of SRH among participants with HF to that of participants with different types of incident disease, such as those who remain disease-free throughout follow-up and those who experience myocardial infarction, stroke, lung cancer, or receive a cardiac procedure.

Aim 3b: Determine whether the relationship is modified by the presence or absence of chronic conditions or by age, race/study community, gender or individual SES.

We hypothesize that participants of lower neighborhood SES will have a steeper slope of decline in SRH across time compared to participants of higher neighborhood SES. It is possible the effect of low neighborhood SES will be modified by other sociodemographic or socioeconomic variables, resulting in more of a decline in SRH over time among these participants.

III. BACKGROUND AND SIGNIFICANCE

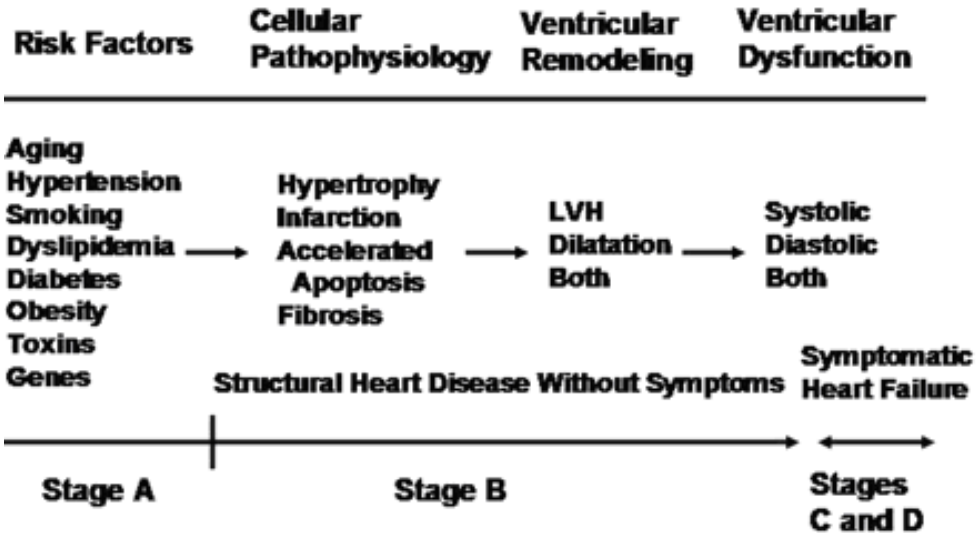
A. Epidemiology of Heart Failure

HF is a complex medical syndrome that has major personal, public health and economic implications. HF does not have a single pathophysiologic etiology (Mosterd & Hoes, 2007; Schocken et al., 2008). The most common etiology in industrialized societies is ischemic heart disease (IHD). Other potential causes include hypertension, valvular heart disease, arrhythmias such as atrial fibrillation, and alcohol abuse (Levy et al., 2002; Mosterd & Hoes, 2007).

The global diffusion of coronary heart disease (CHD), including HF, is likely a result of population aging and improved treatment and survival of patients with CHD (Schocken et al., 2008). In the United States (US), a growing burden of HF is anticipated as the population of persons 65 years and older is expected to exceed 70 million by the year 2030 (DHHS, 2007). The lifetime risk of HF is an estimated 20% for both men and women (D. M. Lloyd-Jones et al., 2002). Approximately 5.2 million people in the US have HF (Thom, 2007), and CHD is the leading cause of hospitalization in the US (Popovic & Hall, 2001). The American Heart Association estimates that more than $33 billion in medical expenditures were attributable to HF in 2007 (Rosamond et al., 2007), and that number is expected to increase with the increasing burden of the disease.

Four clinical stages of HF have been identified by the American Heart Association (AHA)/American College of Cardiology (ACC) (**Figure 3.1**) (Schocken et al., 2008). As seen in **Figure 3.1**, Stage A represents preclinical disease, and includes CHD risk factors such as aging, hypertension, smoking, diabetes mellitus and obesity. The accumulation of risk factors in Stage A leads to and exacerbates structural changes in the heart during Stage B. The preclinical progression of HF from Stage A to Stage B may, for example, involve the occurrence of myocardial infarction (MI) which, on a cellular level, affects the efficiency of the heart via increased collagen synthesis (i.e., myocardial fibrosis) and decreased contractility of the myocardium. Stage B captures the early stages of decompensation, in which the heart structure changes in order to adapt to consequences of CHD and ischemia and maintain cardiac output. In Stages C and D, structural heart disease is accompanied by clinical signs and symptoms of ventricular dysfunction.

Figure 3.1. Four clinical stages of heart failure, AHA/ACC



(Schocken et al., 2008)

Patients diagnosed with HF often have a high burden of clinical comorbidities. Chronic conditions such as hypertension, MI, diabetes and obesity are risk factors for the development of HF (Schocken et al., 2008; Weir, McMurray, & Velazquez, 2006), and clinical HF is commonly accompanied by these factors (Heywood et al., 2007). In a scientific statement, the AHA names precursors to HF (e.g., hypertension and CHD) as targets for HF prevention (Schocken et al., 2008). Registry studies indicate that, of patients hospitalized for HF, more than 50% had coronary artery disease, 27-44% had type-2 diabetes, nearly 75% had hypertension and 18-30% had renal insufficiency (Adams et al., 2005; M. S. Nieminen & Harjola, 2005). Further, risk factors for conditions comorbid with HF are more common among patients of low SES. In a study of residents of Rome aged 75 and older, Antonelli-Incalzi et al. found that decreasing neighborhood SES was associated with an increase in all-cause readmission rate, hospital length of stay and comorbidity, as defined by the Charlson index of comorbidity (Antonelli-Incalzi et al., 2007). Data from the Behavioral Risk Factor Surveillance System, which were age-standardized to the year 2000 US population, report the prevalence of CHD risk factors by level of education, income and employment status, and show an inverse relationship between the prevalence of CHD risk factors and individual-level SES (**Table 3.1**).

Table 3.1. Prevalence (%) of coronary heart disease risk factors* by sociodemographic characteristics, Behavioral Risk Factor Surveillance System, United States, 2003

Characteristic	%	Characteristic	%
Age group (years)		Annual household income	
35-49	34.6	<$10,000	52.5
50-64	51.1	$10,000-19,999	49.3
≥65	56.4	$20,000-34,999	42.8
Race/ethnicity		$35,000-49,999	37.0
White, non-Hispanic	35.5	≥$50,000	28.8
Black, non-Hispanic	48.7	Employment status	
Sex		Employed	34.0
Men	37.8	Unemployed	43.4
Women	36.4	Homemaker	34.3
Education		Retired	45.1
Less than high school	52.5	Unable to work	69.3
High school or equivalent	43.8		
Some college	36.9		
College graduate	25.9		

*Age-adjusted
(CDC, 2005)

Low SES has been associated with higher HF incidence (He et al., 2001; Ingelsson, Lind, Arnlov, & Sundstrom, 2006; F. A. McAlister et al., 2004; Schaufelberger & Rosengren, 2007; S. Stewart et al., 2006). In addition, there remain differences in HF morbidity and mortality which are unexplained by clinical features of the disease (Fonarow, 2008), suggesting the need to explore other domains to understand the progression of HF. Identifying social and economic neighborhood forces which independently impact health would have important implications for the management and treatment of HF patients (Chaix et al., 2007; Stjarne et al., 2006). It is likely that the neighborhood SES of an area determines the availability of health care resources in a community, such as the proximity of neighborhood health clinics. Outpatient care in local health clinics is critical to the out-of-hospital monitoring of HF patients, and if not available in low neighborhood SES areas, may adversely affect the prognosis of HF patients in that community (G. Lee & Carrington, 2007). It remains to be seen if living in a low neighborhood SES area imparts risk of poor HF prognosis above and beyond that influenced by individual SES and comorbid conditions.

B. Heart Failure Progression

The benefits of HF care, including pharmacologic therapies (Bohm, Maack, Wehrlen-Grandjean, & Erdmann, 2003; Ferreira, Bettencourt, Cortez, Araujo, & M., 1997; Hjalmarson et al., 2000; Jamali, Tang, Khot, & Fowler, 2001; Packer et al., 1996; Packer et al., 2001; Pitt et al., 1999), diagnostic and invasive (Guru et al., 2007; Udell et al., 2007) procedures, likely extend to patients in the early stages of HF by treating risk factors and preventing or slowing progressive changes in heart structure and function. The prescription of HF therapies such as angiotensin converting enzyme (ACE) inhibitors, beta (β)-blockers, diuretics and digoxin are supported by the AHA/ACC and European Society of Cardiology guidelines, as are certain diagnostic and invasive procedures (Hunt et al., 2001; Remme & Swedberg, 2002). However, in the Initiation Management Predischarge process for Assessment of Carvedilol Therapy for Heart Failure (IMPACT-HF) registry, in 30 US hospitals, 60-day death or rehospitalization exceeded 30%, despite the use of evidence-based therapies, such as ACE inhibitors, digoxin and β-blockers (O'Connor, Stough, Gallup, Hasselblad, & Gheorghiade, 2005). Thus, there exists a need to exploe other factors which may influence the progression of HF, such as sociodemographic and SES variables.

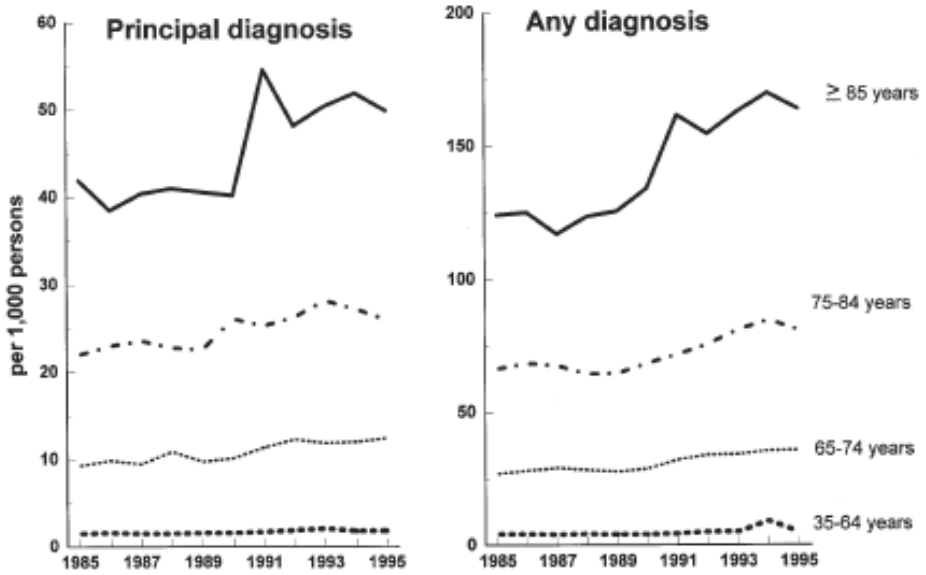
Mechanisms by which low SES may result in adverse health outcomes have been explored in the literature. Lack of access to financial resources, for example, has been shown to decrease the ability of female diastolic HF patients to perform self-care practices, such as medication adherence and daily weighing, and increase their likelihood of negative clinical outcomes, including rehospitalization (Gary, 2006). Meanwhile, higher education and HF symptom severity were positively correlated with self-care, and may influence medication adherence for comorbid conditions such as diabetes and hypertension (He et al., 2001;

Rockwell & Riegel, 2001). Further research indicates that lacking a prescription benefit, having lower income, fewer assets and worse health status are associated with an inability to afford medications and may result in coping behaviors such as taking medication every other day instead of daily to make the prescription last longer (Saver, Doescher, Jackson, & Fishman, 2004).

1. Rehospitalization

HF accounts for 12 to 15 million physician visits and 6.5 million hospital days per year, and is the leading cause of hospitalization among patients 65 and older in the US (Goff, Pandey, Chan, Ortiz, & Nichaman, 2000; M. S. Nieminen & Harjola, 2005). Hospitalizations for HF in the US reached 1.1 million in 2004 (Rosamond et al., 2007), and National Hospital Discharge Survey (NHDS) data show that annual hospitalizations with HF listed as primary or secondary diagnoses are increasing over time (Blustein, Hanson, & Shea, 1998; Haldeman et al., 1999) (**Figure 3.2**). Fang et al. reported that hospitalizations with any mention of HF on NHDS records tripled from 1.3 to 3.9 million from 1979 to 2004 in the US (Fang et al., 2008). It is estimated that more than 75% of the $10 billion spent to manage HF each year is used to cover the cost of hospitalization (Polanczyk, Newton, Dec, & Di Salvo, 2001; Zannad, Adamopolous, Mebazaa, & Gheorghiade, 2006).

Figure 3.2. Prevalence of hospitalization of patients with heart failure in the US (per 1,000 persons) as a principal (first-listed) or any listed diagnosis, by year and age group



(Haldeman et al., 1999)

In a review of 31 research reports from 1986 to 2004, one-third of HF patients were rehospitalized three to six months after discharge (Anderson et al., 2006). Rehospitalization rates are shown to be higher among older patients, non-Whites, and patients with prior hospitalizations and multiple primary care visits (Fang et al., 2008; Ghali et al., 1990; Inouye et al., 2008; Schocken et al., 2008). Several studies have reported a combined endpoint of rehospitalization or mortality. In those analyses, prevalence of rehospitalization or death at 60 days was 31-35% (Felker et al., 2004; O'Connor et al., 2005), and 81% (Zannad et al., 1999) at one year.

Repeat hospitalizations following a diagnosis of HF are common, are due to a worsening of HF symptoms or other clinical comorbidities, and are a burden on the health care system (MedPAC, 2007). A high number of repeat hospitalizations for HF and a short interval of time between subsequent hospital readmissions may be indicators of poor patient health and more severe disease. High readmission rates may also be an indication of limited outpatient

treatment options in the community or the treatment received during a hospital admission not resulting in sustained, adequate out-of-hospital management of HF symptoms (Adams et al., 2005; Cuffe et al., 2002; Krumholz et al., 1997).

Hospital discharges for HF have increased 157% from 1979 to 2002 (*Heart Disease and Stroke Statistics - 2005 Update*, 2005), and many rehospitalizations for HF are likely preventable (MedPAC, 2007). Repeat hospitalizations among patients with HF may account for the growing burden of hospitalized HF cases, with up to 40% of patients being readmitted within six months (Hoyt & Bowling, 2001). Due to limited follow-up, extant research has not adequately described the burden of repeat hospitalizations among HF cases.

Studies conducted to date are rich in clinical data, however, they are limited by short-term follow-up analyses of HF progression. Longer follow-up is needed to adequately capture the rehospitalization experience for the majority of patients diagnosed with this chronic disease. Since HF is a chronic disease, it is important to allow for adequate follow-up in order to describe the clinical course of HF progression. In addition, rehospitalization is often treated as a secondary aim in clinical trials or a composite endpoint with mortality. Rates of rehospitalization are measured in these studies as calculated from the time of randomization, not the date of the incident HF event. Patients in clinical trials are also healthier than patients not enrolled in clinical trials, with fewer comorbidities. As a result, 60- to 90-day rehospitalization rates reported in these trials are likely an underestimate with respect to the general population of patients with HF.

The proposed research is not limited to a clinical trial design, and will address the aforementioned limitations by describing the rehospitalization experience of HF patients

independent of mortality. In addition, incident hospitalized HF will be a clearly delineated starting point from which patients will be followed over many years for repeat hospital admissions. Further, HF patients will not be excluded from the analysis due to a high burden of comorbidity, rather, the extent of comorbidity will be considered during data analysis in order to make the findings generalizable to a broader population of HF patients.

2. Mortality

In addition to being recognized as a major cause of serious morbidity (Adams et al., 2005; Cowie et al., 2002; H. Eriksson, 1995; Hoyt & Bowling, 2001), HF mortality is high (Jong et al., 2002; M. S. Nieminen & Harjola, 2005). It is estimated that more than 300,000 deaths are attributed to HF as a primary or contributory cause each year in the US, regardless of advances in treatment (Hunt et al., 2001). HF mortality rates increase sharply with age. In 1995, HF mortality rates per 100,000 US population were 633.5 for persons aged greater than or equal to 85 years, 130.8 for persons aged 75-84 years, and 32.2 for persons aged 65-74 years (Haldeman et al., 1999). In a study of five-year mortality in Scotland, HF was associated with the poorest survival, with the exception of lung cancer, with which it shared a similar number of lost life-years (Simon Stewart et al., 2001).

From 1980 to 1995, the number of deaths in the US with an underlying cause of HF increased nearly 70% (Haldeman et al., 1999). While mortality rates for HF remain relatively high during in-hospital, 30-day, one-year and five-year periods, age-adjusted mortality rates appear to be declining slightly over time (John G. F. Cleland, Gemmell, Khand, & Boddy, 1999; Haldeman et al., 1999; MacIntyre et al., 2000; Roger et al., 2004). Jong et al. noted that 30-day and one-year mortality rates among unselected patients

hospitalized for incident HF were higher than those reported in clinical trials, except for the youngest patients with a low level of comorbidity (Jong et al., 2002). As such, the decline witnessed in HF mortality tends to be more dramatic among patients in clinical trials compared to community trials, and in men compared to women (Roger et al., 2004; Schocken, Arrieta, Leaverton, & Ross, 1992).

In-hospital HF mortality ranges from 3-18% (Adams et al., 2005; J.G.F Cleland et al., 2003; Cowie et al., 2002; Gheorghiade et al., 2006; Khand, Gemmell, Rankin, & Cleland, 2001; Markku S. Nieminen et al., 2006; M. S. Nieminen & Harjola, 2005; O'Connor et al., 2005; Reitsma et al., 1997). Meanwhile, 30-day mortality is approximately 20% (Cowie et al., 2002; MacIntyre et al., 2000), while one-year mortality ranges from 30-50% (Jong et al., 2002; MacIntyre et al., 2000; Packer et al., 2001; S. Stewart et al., 2002) and five-year mortality often exceeds 50% - and has approached 80% (Gomberg-Maitland, Baran, & Fuster, 2001; Ho, Anderson, Kannel, Grossman, & Levy, 1993; MacIntyre et al., 2000; Owan et al., 2006; Shahar et al., 2004). Previously published data from the Atherosclerosis Risk in Communities (ARIC) study (1987-2002), show that 30-day mortality among cohort members was 10%, while one- and five-year mortality was 22% and 42%, respectively (Loehr, Rosamond, Chang, Folsom, & Chambless, 2008).

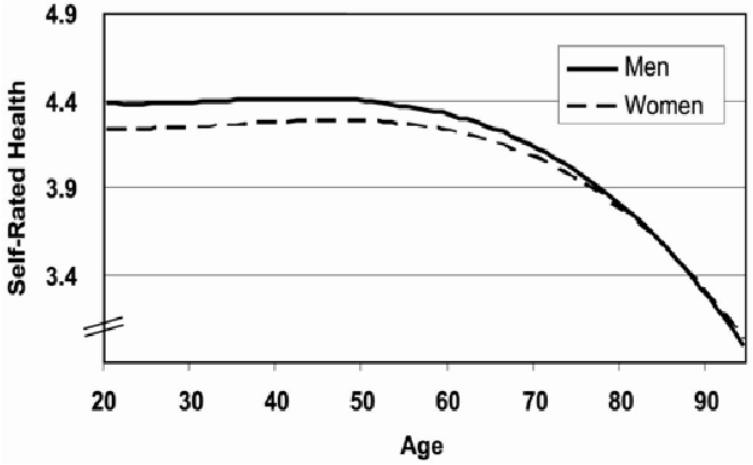
The definition of HF between studies differs considerably, whether based on HF signs and symptoms or diagnoses received in-hospital. The varied definitions of HF would likely be reflected in different mortality outcome measurments. It is also possible that the wide range of mortality estimates is due to an inconsistent measure of the timing of the incident HF event. For example, while cohort studies are often able to calculate mortality from a first diagnosis of HF during a clinic visit or hospitalization, many registry-based or clinical trials

report mortality rates measured from the time of enrollment rather than the time of initial diagnosis.

3. Self-rated Health

SRH is thought to reflect both mental and physical health domains, and is assessed by asking individuals to objectively describe their health status on a four- to eight-point Likert scale (e.g., excellent, good, fair or poor)(Singh-Manoux et al., 2007). Questions posed to study participants may refer to "general health status" or "health", or may differ by whether or not they ask for SRH in comparison to others one's age, yet different measures tend to produce similar responses (I. Eriksson, Unden, & Elofsson, 2001). SRH responses are typically stable until age 50 (McCullough & Laurenceau, 2004), and decline with age(McFadden et al., 2008). Researchers hypothesize that responders of younger ages tend to be relatively free of illness and disability, whereas during later years, lower SRH reflects an uncertainty or even pessimism regarding one's health status, or lower SRH may even be a response to other major life events, such as retirement (McCullough & Laurenceau, 2004). McCullough and Laurenceau conducted a multilevel analysis of annual measures of SRH among 1,411 men and women aged 20-94 years in the Terman Life Cycle Study of Children with High Ability, and graphed the curvilinear natural history of SRH. They found that men reported higher SRH compared to women prior to age 50, and that SRH declined steeply for both sexes after age 50 (McCullough & Laurenceau, 2004) (**Figure 3.3**).

Figure 3.3. Trajectory of SRH across adulthood: Terman Life Cycle Study of Children with High Ability, 1940-1999



(McCullough & Laurenceau, 2004)

SRH has been found to be associated with adverse health outcomes, such as repeated hospitalizations (Kennedy, Kasl, & Vaccarino, 2001), and mortality (Wolinsky et al., 2008). Among adults aged 65 years and older, high self-efficacy and favorable perception of neighborhood conditions was associated with better SRH status (Bowling, Barber, Morris, & Ebrahim, 2006). Kennedy et al. investigated the effect of a single baseline measurement of SRH on future hospitalizations, and found that a good SRH was associated with a decreased risk of a first HF hospitalization as well as first and second hospitalizations for any cause (Kennedy et al., 2001). Additionally, Diehr and colleagues found that SRH declined gradually among participants in the Cardiovascular Health Study, who had a mean age of 73 at baseline, until a year before death, and then droped sharply (P. Diehr, Williamson, Patrick, Bild, & Burke, 2001). Thus, it is hypothesized that a report of poor SRH may be able to predict adverse health outcomes.

Many studies have investigated factors associated with current SRH (Daponte-Codina et al., 2008; McFadden et al., 2008; Wight et al., 2008) or a change in SRH from baseline

(Wolinsky et al., 2008), yet few studies have reported the trajectory of repeated measures of SRH across some specified time period in order to describe the progression of disease (P. Diehr et al., 2001). Studies by Wight et al., McFadden et al. and Daponte-Condina et al. dichotomized SRH into *fair or poor* (vs. *good* or *excellent*), *poor or moderate* (vs. *good* or *excellent*) and *less than good* (vs. *good*) health, respectively (Daponte-Codina et al., 2008; McFadden et al., 2008; Wight et al., 2008). The analytic technique of collapsing the SRH categories is likely to obscure important differences between persons with *excellent* compared to *good*, and *fair* compared to *poor* health.

Meanwhile, Wolinsky et al. (Wolinsky et al., 2008) reported on changes in SRH among African Americans over a four-year period. Participants were classified into one of three categories: improved, declined and no change in SRH since baseline. Participants with HF at baseline were more likely to report improved SRH, compared with no change in SRH, over the four years of follow-up (Wolinsky et al., 2008). However, Wolinsky et al. censored participants from the analysis upon their death, so while participants with HF were more likely to improve their SRH status, they may have also been more likely to die during follow-up, thus biasing the results with responses from healthy survivors (Wolinsky et al., 2008).

C. Socioeconomic Status

Mechanisms by which low SES may result in adverse health outcomes have been explored in the literature. Lack of access to financial resources, for example, has been shown to decrease the ability of female diastolic HF patients to perform self-care practices, such as checking and recording blood pressure and pulse information each day, and increase their likelihood of negative clinical outcomes, including rehospitalization (Gary, 2006).

Meanwhile, education and HF symptom severity were positively correlated with self-care, and may influence medication adherence for comorbid conditions such as diabetes and hypertension (He et al., 2001; Rockwell & Riegel, 2001). Further research indicates that lacking a prescription benefit, having lower income, fewer assets and worse health status are associated with an inability to afford medications and may result in coping behaviors such as taking medication every other day instead of daily to make the prescription last longer (Saver et al., 2004).

1. Neighborhood Socioeconomic Status

Health outcomes among persons living in low neighborhood SES areas are often compared to persons living in high neighborhood SES areas. Low neighborhood SES, also referred to as *high socioeconomic deprivation* in the literature, is commonly associated with poor health outcomes. Specifically, living in socioeconomically disadvantaged neighborhoods has been shown to increase the risk of MI as well as the prevalence of and mortality due to CHD (Stjarne et al., 2006). Chaix et al. (2007) found neighborhood SES to be inversely associated with the incidence of and mortality from IHD, after controlling for individual socioeconomic factors (Chaix et al., 2007). To date, few studies have incorporated measures of neighborhood SES in their analyses of HF outcomes.

Neighborhood SES is characterized by indicators of the economic resources available in the community, and is helpful for monitoring socioeconomic disparities in health. It may be defined by criteria such as the average income or educational attainment of the neighborhood residents, or by the percent of owner-occupied housing in the community. For example, median household income of all residents in a geographically defined neighborhood may be

used to represent the amount of collective economic resources for that area (Stjarne et al., 2006).

An alternative viewpoint among researchers regarding the utility of neighborhood SES for monitoring socioeconomic disparities is one of convenience. Many researchers who utilize measures of neighborhood SES do so because they do not have access to measures of individual SES. For example, patient address data are commonly available from the medical record, while individual SES measures (e.g., education, income and occupation) are not. In the current work, measures of neighborhood SES are not intended to be proxies of individual SES. The economic environment of the neighborhood directly and indirectly impacts health via social networks, access to care and to what extent the culture of the neighborhood fosters health promoting behaviors. While neighborhood SES and individual SES may be related in terms of the neighborhood an individual can afford to live in, for example, the location or structure of the neighborhood may benefit or impede its residents with regard to accessing preventive care, healthy foods or recreation regardless of their level of individual SES.

2. Neighborhood Socioeconomic Status and Heart Failure Progression

Low SES is associated with higher HF incidence (He et al., 2001; Ingelsson et al., 2006; F. A. McAlister et al., 2004; Schaufelberger & Rosengren, 2007; S. Stewart et al., 2006), rehospitalization and survival (Philbin, Dec, Jenkins, & DiSalvo, 2001; Rathore et al., 2006; S. Stewart et al., 2002; Simon Stewart et al., 2001; Wen & Christakis, 2005). Researchers have found that neighborhood SES has an effect on a patient's health independent of individual SES (Pickett & Pearl, 2001; Robert, 1999; Yen & Kaplan, 1999). Social environment characteristics, such as those imparted by neighborhood SES, have been shown

to be associated with all-cause mortality after adjustment for individual socioeconomic and demographic factors (Yen & Kaplan, 1999). The independent influence of neighborhoods may be due to issues of access to care, structural social support, and the built environment. Others suggest the influence of neighborhood SES on health is determined by material and infrastructure resources available in the community which serves to strengthen the effects of social stratification (Chaix et al., 2007; Stjarne et al., 2006).

The influence of social neighborhood context on the progression of HF is one domain that has been understudied. Evidence suggests that social and environmental contexts play an important role in health outcomes (Nancy Krieger et al., 2002; Marmot, 2003). However, low individual SES is also associated with poor health outcomes when neighborhood SES is not taken into account. For example, less than 12 years of education, a marker of low individual SES, was found to be associated with a higher burden of CVD and related risk factors (Mensah, Mokdad, Ford, Greenlund, & Croft, 2005) and an increased number of hospitalizations among ambulatory HF patients (Sui, Gheorghiade, Zannad, Young, & Ahmed, 2007). An additional study in Japan found the odds of rehospitalization increased among patients with no occupation and poor follow-up care (Tsuchihashi et al., 2001). To date, the influence of neighborhood socioeconomic factors on HF progression have not been assessed in the context of both individual SES and demographic factors.

i. Neighborhood Socioeconomic Status and Rehospitalization

Blair (2002) reviewed eight published manuscripts on the relationship between area-level measures of social deprivation and rehospitalization rates for HF. It was concluded that hospital admission rates increase with increased social deprivation (Blair, Lloyd-Williams, &

Mair, 2002). McAlister (2004) reported follow-up rates with primary care physicians were lowest among patients of high socioeconomic deprivation, as measured at the neighborhood level (F. A. McAlister et al., 2004). Fewer primary care visits may be an indication for higher hospital utilization rates among patients of low neighborhood SES.

Neighborhood SES may affect susceptibility to readmission among patients with HF (Pickett & Pearl, 2001; Robert, 1999; Yen & Kaplan, 1999). Higher rates of hospital readmission have been observed among socially deprived groups (Antonelli-Incalzi et al., 2007; Blair et al., 2002; F. A. McAlister et al., 2004; Philbin et al., 2001; Rathore et al., 2006; Wen & Christakis, 2005). In contrast, high neighborhood SES patients have a lower frequency of rehospitalization and a higher likelihood of survival after an incident hospitalization, after adjusting for other patient characteristics (Philbin et al., 2001; Rathore et al., 2006; S. Stewart et al., 2002; Simon Stewart et al., 2001; Wen & Christakis, 2005).

The influence of the neighborhood context on a variety of CHD outcomes has been demonstrated in previous neighborhood SES research conducted in ARIC community surveillance (Foraker et al., 2008; K. M. Rose et al., 2007). Public health interventions on a neighborhood scale have the potential of reaching a large number of patients in need. For example, if neighborhood of residence is shown to play a role in the patterns of rehospitalizations among HF patients, community-level interventions, such as providing transportation to local health clinics or mobile health units for the monitoring of HF patients can be employed.

ii. Neighborhood Socioeconomic Status and Mortality

In a nationwide US study of all-cause and cause-specific mortality, Jemal et al. (2008) estimated that 48% of deaths among men and 38% of deaths among women aged 25-64 years would not have occurred if all adults, regardless of educational attainment, had experienced the death rates of college graduates (Jemal et al., 2008). In the literature, the association between SES and HF mortality is inconsistent, and there exist a paucity of data regarding estimates of mortality arising from an incident HF diagnosis. In a review of eight clinical studies, lower SES was associated with increased mortality among HF patients (Blair et al., 2002). In particular, one-year mortality due to CHD is associated with neighborhood-level SES. Winkleby et al. (2007) found an increased likelihood of one-year CHD mortality among 130,024 women and men in Sweden living in low neighborhood SES compared to high neighborhood SES areas (Winkleby, Sundquist, & Cubbin, 2007). This relationship remained significant after controlling for age, marital status, family income, educational attainment, immigration status, time lived in neighborhood, and urban/rural status (Winkleby, Sundquist, & Cubbin, 2007).

Meanwhile, in a registry of 12,220 incident HF cases in the United Kingdom, 30-day, one-year and five-year survival were not influenced by neighborhood SES, as measured by quintiles at the postcode level (Blackledge, Newton, & Squire, 2003). In a smaller study conducted in London, neighborhood SES, as measured by the Jarman index at the postcode level, was not found to be associated with one-year mortality (Cowie et al., 2002). While the aforementioned studies have reported an inverse association between neighborhood-level SES and mortality, these studies from the United Kingdom have not. The disparate findings may have to do with the level of aggregation of neighborhood-level SES provided by the

postcode. For example, in the United Kingdom, the postcode is unique to 15 or 20 households (Danesh et al., 1999) and is conceptualized as a useful marker of individual SES since it applies to so few households. Thus, the interpretation of neighborhood-level effects while using postcode as the level of aggregation may not be valid.

In a study of 10,557 Medicare beneficiaries in Chicago (1993-1999), higher SES was associated with longer survival post-hospitalization for five clinical conditions (Wen & Christakis, 2005). Wen and colleagues reported a statistical interaction between neighborhood SES (zip-code level data) and individual SES (poverty status), indicating that high neighborhood SES particularly benefited patients with high individual SES, especially among MI patients (Wen & Christakis, 2005). With regard to individual SES, Brazilian HF patients receiving public health system (vs. private insurance) care experienced greater mortality (de Campos Lopes, Yamada, Araujo, Pereira Barreto, & Mansur, 2006). In addition, individual SES, as measured by educational attainment and financial distress, was significantly associated with all-cause mortality and the endpoint of death or rehospitalization in the Studies of Left Ventricular Dysfunction trial (Dries et al., 1999). Similar to studies of rehospitalization, studies of the neighborhood SES-HF association typically do not include measures of individual SES, precluding inferences regarding the robustness in predictive power of neighborhood SES and its associated constructs.

An additional consideration in the study of HF mortality is that combining new-onset and worsening HF in order to assess mortality serves to confound the effects of new versus recurrent disease on mortality (Rudiger et al., 2005). The existing literature not only lacks consistency regarding an adequate quantification of incident HF and related mortality rates, but many studies are also constrained by short follow-up time.

iii. Neighborhood Socioeconomic Status and Self-rated Health

Cross-sectional analyses among elderly persons consistently demonstrate that living in disadvantaged neighborhoods, having low education and low household wealth increase the odds of reporting poor health (Daponte-Codina et al., 2008; Kunst et al., 2005; Power, Rodgers, & Hope, 1998; Wight et al., 2008). In a study of the relation between neighborhood SES (percent of residents living below poverty) and SRH among rural women without a history of breast cancer in North Carolina, individual SES (family income) was found to be an effect measure modifier (Kobetz, Daniel, & Earp, 2003). As a result, women from high-poverty neighborhoods experienced 35% greater odds of low SRH compared to women from low-poverty neighborhoods, and within low-poverty neighborhoods, low-income women had 40% higher odds of low SRH than high-income women. In other studies, the association between neighborhood SES and SRH appears to persist after taking individual SES into account (Wight et al., 2008).

Proposed mechanisms of the neighborhood SES-SRH relationship include an increase in allostatic load due to the stressors of low SES, and few resources available to persons from low neighborhood SES areas in order to deal with such stress (Wight et al., 2008). Few studies utilize longitudinal data to explore changes in SRH (Paula Diehr, Johnson, Patrick, & Psaty, 2005; Paula Diehr & Patrick, 2003; P. Diehr et al., 2001), and no research has been done to date to quantify the trajectory of repeated measures of SRH among HF patients by neighborhood SES. Information regarding SRH trajectories that differ by SES may be used to develop interventions which prevent the loss of well-being associated with an incident diagnosis of HF and which may delay subsequent adverse health events, such as rehospitalizations or mortality.

3. Medicaid Status

Medicaid enrollment is often used as a surrogate for low individual SES in studies of hospital claims data (Croft et al., 1999). A study of Medicaid recipients from four US states (Arkansas, California, Indiana and New Jersey) indicated that Medicaid enrollees are most likely to be aged 64 years or less, white and female (Esposito, Bagchi, Verdier, Bencio, & Kim, 2009). However, in a US-wide review of 1.2 million hospital Medicare claims for HF in 1986, black patients were three times as likely as whites, and females twice as likely as males, to be eligible for Medicaid (Croft et al., 1999). Thus, the demographic distribution of Medicaid recipients differ by region.

Health insurance status may be associated with care-seeking behavior (Philbin & DiSalvo, 1999) and subsequent disease outcomes (Ayanian et al., 1993). Medicaid, in particular, may exert effects on health outcomes which are independent of neighborhood-level SES (Foraker et al., 2008; Ross & Mirowsky, 2000), as its receipt is determined by having certain diseases and disabilities or an income below the poverty line (Ku, 2005; Rosenbaum, 2002). Thus, in in the absence of other individual-level SES information, Medicaid coverage is a reasonable surrogate for low SES.

The Center for Medicaid and Medicare Services has targeted HF for cost-saving measures, as HF is the most common cause of hospitalization among older US adults (Mehrotra, McNeil, & Landon, 2007). During the last decade, chronic disease management programs have addressed patient self-care and provider guideline adherence in order to keep HF patients out of the hospital and to reduce health care costs for both HF and diabetes (Katz et al., 2009; Mehrotra et al., 2007). One such chronic disease management program

implemented in Indiana resulted in a decrease in claims paid for Medicaid recipients with HF (Katz et al., 2009). Based on a survey of 120 health plans following a mandate for chronic disease management programs, the authors concluded that the success of such programs to decrease health care costs among HF patients depends upon the engagement of health care providers in guideline-based care (Mehrotra et al., 2007).

4. Medicaid Status and Heart Failure Progression

Evidence suggests that social and environmental contexts play an important role in health outcomes (Ana V Diez Roux, Borrell, Haan, Jackson, & Schultz, 2004; Nancy Krieger et al., 2002; Marmot, 2003). Although health insurance is one facet of the social context, research to date has not assessed the influence of Medicaid enrollment on the risk of rehospitalization or mortality among HF patients in the context of individual socioeconomic, demographic and comorbid factors.

i. Medicaid Status and Rehospitalization

Compared to patients hospitalized for HF with other types of insurance coverage, Medicaid patients experienced the longest length of stay, greatest amount of hospital charges and the highest readmission rate for HF in New York state in 1995 (Philbin & DiSalvo, 1998). An additional finding in this study was that discharge code *428* was found in the principal diagnosis position for 87% of all patients, and the presence of this code was equally common among insurance groups (Philbin & DiSalvo, 1998). Therefore, there does not appear to be a discharge code usage preference by insurance type in capturing HF as the reason for hospital admission.

Meanwhile, medication adherence appears to influence readmission rates among Medicaid recipients. In a study of Medicaid beneficiaries with HF from four US states, nearly 30% of Medicaid beneficiaries from four states had coexisting coronary artery disease or diabetes, and those who were adherent to HF medications experienced fewer hospitalizations and were less likely to visit the emergency department compared to those who were nonadherent (Esposito et al., 2009).

ii. Medicaid Status and Mortality

In a study of managed care patients hospitalized for HF in New York state in 1995, Medicaid patients did not experience an increased risk of mortality during the index HF hospitalization compared to patients with other types of insurance coverage (Philbin & DiSalvo, 1998). Similar findings of no difference in in-hospital mortality rates among Medicaid recipients were reported from a study of managed care in Oregon during the same year (Ni, Nauman, & Hershberger, 1998). Meanwhile, a paucity of data exists which takes into account a longer period of follow-up to determine if Medicaid enrollees experience an increased risk of mortality post-discharge.

Differences in the rates of rehospitalization or death among Medicaid recipients may exist by race and comorbidity burden. Croft and colleagues (1999) identified 170,239 Medicare patients who were hospitalized for HF after being free of HF during the previous two years. An increased six-year risk of death was seen among black, but not white, Medicaid enrollees (Croft et al., 1999). In addition, HF patients with comorbid diabetes had a higher risk of death compared to patients without diabetes listed as a concurrent condition during the index hospitalized HF event (Croft et al., 1999).

5. Potential Role of Comorbid Conditions

Chronic comorbid conditions likely play an important role in the pathophysiology and progression of HF. For example, chronic kidney disease (CKD) manifests in elevated or worsening blood pressure, which may in turn reduce cardiac output due to vascular restriction. CKD may also create an excess of fluid due to reduced excretion (i.e., preload) resulting in cardiac remodeling (Kottgen et al., 2007). In turn, hypertension is a risk factor for Stage A HF according to the AHA/ACC guidelines (**Figure 3.1**), and cardiac adaptations to volume overload allow for preclinical progression through Stage B to the clinical symptoms of stages C and D.

It is estimated that CHD is the most common cause of left ventricular systolic dysfunction (LVSD) leading to HF in industrialized societies (John G F Cleland, John, Dhawan, & Clark, 2001; Hunt et al., 2001), and Cowie et al. (2002) found that patients developing HF in the context of MI had a worse prognosis compared to patients with other etiologies (Cowie et al., 2002). A two- to four-fold increase in in-hospital mortality has been shown in patients with HF occurring after acute MI (Weir et al., 2006), and both 30-day and one-year mortality following a first HF diagnosis increases in the highest comorbidity-laden groups (Jong et al., 2002; Simon Stewart et al., 2001).

Research from the Acute Decompensated Heart Failure National Registry (ADHERE) reported 21% of patients had serum creatinine levels greater than 2 mg/dL(Adams et al., 2005). Worsening renal failure is associated with poor HF outcomes. A commonly utilized measure of kidney function, glomerular filtration rate (GFR), is estimated using a patient's serum creatinine level. In the literature, there exists an inverse association between GFR and

mortality (Hillege et al., 2000; Jong et al., 2002; Smith et al., 2005). The ADHERE has identified creatinine level as a strong predictor of in-hospital mortality among HF patients (Marie Galvao et al., 2006), and Heywood et al. (2007) hypothesize that GFR is more predictive of mortality than LVSD in patients with HF (Heywood et al., 2007). Anderson et al. (2006), in a review of 31 research articles of HF readmission, concluded that conditions such as diabetes and renal failure may rapidly advance HF and contribute to more severe disease (Anderson et al., 2006; Go et al., 2006; Khand et al., 2001; Remme & Swedberg, 2002).

ACC/AHA guidelines suggest that the evaluation and management of comorbid disease, such as diabetes and kidney disease, in HF patients may be as critical as the treatment of HF itself (Hunt et al., 2001). Although comorbid conditions appear to be important in the progression of HF, many studies omit the study of selected comorbidities (Blackledge et al., 2003; B. H. Greenberg et al., 2007) or patients with significant comorbidity from analyses entirely (Felker et al., 2004; Heywood et al., 2007; Rathore et al., 2006).

Comorbid conditions are important to consider in the context of HF progression. Multiple or severe comorbidity may lead to increased rehospitalization, higher mortality or an accelerated decline in SRH, especially in the context of low neighborhood SES. Overall, neighborhood-level SES has been found to be negatively associated with the metabolic syndrome (Ana V. Diez Roux, Jacobs, & Kiefe, 2002) and diabetes (Barker, Gardner, & Power, 1982; Green, Hoppa, Young, & Blanchard, 2003), as well as CHD (Ana V. Diez-Roux et al., 2001; Diez-Roux et al., 1997) and obesity (Boardman, Saint Onge, Rogers, & Denney, 2005). For the aforementioned conditions, low neighborhood SES remained statistically significantly associated with an increase in negative health outcomes, even with

statistical adjustment for individual SES (Daniel, Moore, & Kestens, 2008). The proposed mechanisms allowing neighborhood SES to influence the development of cardiometabolic diseases include maladaptive biologic responses to, and the conscious perception of, chronic and acute stressors (Daniel et al., 2008).

According to published research, it is likely that patients of low neighborhood SES carry a higher burden of comorbidity than patients of high neighborhood SES. Since a higher burden of comorbidity is more common among patients of low SES (Antonelli-Incalzi et al., 2007), it is possible that HF patients of low neighborhood SES with a high level of comorbidity, for example, are at greater risk of mortality within one year compared to HF patients of low SES with a low level of comorbidity. Patients of low neighborhood SES often do not have the neighborhood structural resources (e.g., decreased proximity to local health clinics, pharmacies or access to transportation) or adequate social support (e.g., reside alone, are of older age, do not live among neighbors of high health literacy) to obtain adequate out-of-hospital management of their comorbidities.

Results from studies based on highly selected patient groups cannot speak to the breadth of the burden of HF, and may be underestimating both rehospitalization and mortality rates while only capturing the quality of life/SRH experience of the healthiest patients. As a result, registry studies and clinical trials which exclude patients with a high burden of comorbidity may be omitting a segment of the HF population who would benefit most from public health intervention.

i. Charlson Index of Comorbidity

The Charlson index of comorbidity (**Table 3.2**) has been validated and is used to quantify the burden of comorbidity in several studies of mortality and adverse health outcomes (Charlson, Pompei, Ales, & MacKenzie, 1987). In its use with HF outcomes, a "modified" Charlson index excludes chronic heart failure from the conditions used to compute the comorbidity score (Senni et al., 2006). Overall, mortality (Charlson et al., 1987; Deyo, Cherkin, & Ciol, 1992; Jong et al., 2002) and rehospitalization (Philbin & DiSalvo, 1999) increases with increasing comorbidity index values. However, when applied to Medicare data in Arkansas, the comorbidity index did not predict short-term mortality as well as it predicted long-term mortality (Cleves, Sanchez, & Draheim, 1997). The Charlson-Deyo index of comorbidity applied International Classification of Diseases, Version 9, Clinical Modification (ICD-9-CM) codes to the components of the Charlson index (Deyo et al., 1992). Utilizing a scale of zero, one, two or three or more for the Charlson index, Charlson et al. (1987) concluded that each stepwise increase in the comorbidity index added a similar magnitude of mortality risk as did a decade increase in age (Charlson et al., 1987).

Table 3.2. Charlson comorbidity index, associated discharge codes and point values

Comorbidity category	ICD-9-CM	Description	Value
Myocardial Infarction	410-410.9	Acute myocardial infarction	1
	412	Old myocardial infarction	
Peripheral Vascular Disease	443.9	Peripheral vascular disease, intermittent claudication	1
	441-441.9	Aortic aneurysm	
	785.4	Gangrene	
	V43.4	Blood vessel replaced by prosthesis	
	38.48	Resection and replacement of lower limb arteries	
Cerebrovascular Disease	430-438	Cerebrovascular disease	1
Dementia	290-290.9	Senile dementia Presenile dementia	1
Chronic Pulmonary Disease	490-496	Chronic obstructive pulmonary disease	1
	500-505	Pneumoconioses	
	506.4	Chronic respiratory conditions due to fumes and vapors	
Rheumatologic disease	710.0	Systemic lupus erythematosus	1
	710.1	Systemic sclerosis	
	710.4	Polymyositis	
	714.0-2	Adult rheumatoid arthritis	
	714.81	Rheumatoid lung	
	725	Polymyalgia rheumatica	
Mild Liver Disease	571.2	Alcoholic cirrhosis	1
	571.5	Cirrhosis without mention of alcohol	
	571.6	Biliary cirrhosis	
	571.40-49	Chronic hepatitis	
Diabetes	250-250.3	Diabetes with or without acute metabolic disturbances	1
	250.7	Diabetes with peripheral circulatory disorders	
Moderate or Severe Liver Disease	572.572.8	Hepatic coma, portal hypertension, other sequelae of chronic liver disease, esophageal varices	3
Diabetes with Chronic Complications	250.4-250.6	Diabetes with renal, ophthalmic or neurological manifestations	2
Hemiplegia or Paraplegia	344.1	Paraplegia	2
	342-342.9	Hemiplegia	
Renal Disease	582-582.9	Chronic glomerulonephritis	2
	583-583.7	Nephritis and nephropathy	
	585	Chronic renal failure	
	586	Renal failure, unspecified	
	588-588.9	Disorders resulting from impaired renal function	

(Charlson et al., 1987; Deyo et al., 1992)

Diabetes, a factor in the Charlson comorbidity index, has been shown to increase in-hospital, one-year and five-year mortality and all-cause rehospitalization within 60- and 90-days (B. Greenberg et al., 2006; Ho et al., 1993). Diseases comorbid with HF which are captured in the Charlson index of comorbidity, such as diabetes, may modify the

neighborhood SES-HF progression relationship. For example, if a patient from a low neighborhood SES area also has diabetes, the pathophysiologic consequences of diabetes may lead to more severe disease and a higher likelihood of HF morbidity and mortality compared to patients from low neighborhood SES areas without diabetes, especially considering the importance of having the resources to manage a chronic disease. Suggested mechanisms of this process may include a susceptibility among diabetics to obesity, endothelial dysfunction and LVH (Schocken et al., 2008).

As discussed previously, it is a common practice to exclude patients with selected comorbidities from study, as patients with certain comorbidities may be at greater risk of poor health outcomes. However, since HF is a chronic disease which is often accompanied by comorbid conditions, it is possible that the presence or absence of comorbid disease may affect HF progression. In addition, it remains unknown whether patients of low neighborhood SES who carry a higher burden of comorbidity fare worse compared to patients of low neighborhood SES who carry a relatively lower burden of comorbidity. The investigation of possible effect measure modification of the neighborhood SES-HF progression relationship by comorbidity score does not yet exist in the literature. If it is the case that the Charlson index comorbidity score modifies the neighborhood SES-HF progression relationship, public health interventions to prevent adverse HF outcomes can be further targeted to patients of selected neighborhood SES and comorbidity strata.

ii. Hypertension

A series of NHANES reports document hypertension as an independent risk factor for the development of HF (He et al., 2001), and there is additional evidence that the prevalence

of hypertension among HF patients is increasing over time (Owan et al., 2006). Systemic or pulmonary hypertension can cause cardiac dysfunction due to increased afterload (Schocken et al., 2008). Although hypertension is believed to contribute to ventricular remodeling and the clinical onset of HF, there is a discrepancy in the literature between hypertension as a risk factor for incident HF as compared to HF survival.

In the Organized Program to Initiate Life-saving Treatment In Hospitalized Patients with Heart Failure (OPTIMIZED-HF), patients with lower systolic blood pressure (SBP) upon admission experienced higher in-hospital and 30- to 90-day post-discharge mortality rates (Gheorghiade et al., 2006). Similarly, in a multicenter study of predictors of post-hospitalization mortality (the Finnish Acute Heart Failure Study), three-month, six-month and one-year all-cause mortality decreased with each ten mmHg increase in SBP measured at hospital admission (Siirila-Waris et al., 2006).

Mosterd and Hoes (2007) acknowledge the protective effect of hypertension in their review of the clinical epidemiology of HF, and propose that the unexpected finding may be due to hypotension, or "pump failure", being more unfavorable with respect to HF survival compared to hypertension (Mosterd & Hoes, 2007). It is also possible that the better short-term survival seen among patients with higher SBP upon hospital admission is a result of survivor bias. For example, patients who do not have a life-sustaining SBP may not arrive to the hospital in time to be treated, whereas patients with high SBP may be more likely to be admitted to the hospital alive and receive timely treatment due to their elevated SBP.

Furthermore, in studies of HF, blood pressure data may be limited to that which is collected at the time of hospital admission. It is possible that the SBP reading recorded in the

medical record upon admission is not representative of the patients' typical hypertensive status. Nevertheless, as a result of these apparently conflicting data, an investigation into hypertension as an effect measure modifier of the neighborhood SES-HF progression relationship is warranted.

iii. Overweight and Obesity

Overweight and obesity are well-recognized risk factors for the development of HF (He et al., 2001; Loehr et al., 2008; Loehr et al., 2009; Schocken et al., 2008), however, the existence of overweight/obesity can obscure HF symptoms and may lead to inaccuracies in diagnosing HF (Swedberg et al., 2005). Nonetheless, the physiologic basis for the relationship between overweight/obesity and incident HF is well-defined, and involves an accelerated atherosclerotic process, increased inflammatory response and a predisposition to other chronic diseases (e.g., hypertension, diabetes) which may lead to or exacerbate existing HF (Fonarow, Heywood, Heidenreich, Lopatin, & Yancy, 2007).

Regardless of the suggested pathology linking overweight/obesity with incident HF, in the ADHERE, higher body mass index (BMI) was associated with lower risk of in-hospital and long-term mortality, adjusting for other clinical variables (G. C. Fonarow, J. T. Heywood et al., 2007). The seemingly protective effect overweight/obesity has on HF survival has been termed the "obesity paradox". In addition to the finding that hypertension benefits HF survival, obesity may also be protective in the study of HF survival (Mosterd & Hoes, 2007). These findings suggest that patients with cardiac cachexia, a disease process in which HF patients lose significant non-edematous body mass, are not robust to cardiac events (von Haehling, Lainscak, Springer, & Anker), while patients with excess body weight are not

succeptible to this process. As with comorbid hypertension, no research to date has explored if comorbid obesity modifies the relationship between neighborhood SES and HF progression.

D. Conclusion

As the US population ages, HF will likely continue to be an increasing burden on the individual patient as well as the health care system. The proposed research aims to investigate HF progression in three areas: (1) rehospitalization; (2) mortality and (3) SRH. Specifically of interest is the association between neighborhood SES and HF progression. A conceptual model of the relationship between neighborhood SES and HF progression is shown in **Figure 3.4**.

Demographic characteristics of the patient (age, race / study community and gender) are shown to influence: neighborhood SES, individual SES, presence of clinical comorbidities, health behaviors and HF progression (**Figure 3.4**). Demographic characteristics will be considered in these analyses, but are not the focus of the research, as these factors are not modifiable. Meanwhile, neighborhood SES is shown to influence individual SES, perhaps via educational and occupational opportunities available in the neighborhood, as well as HF progression (**Figure 3.4**). Individual SES is shown to also be associated with neighborhood SES, as individual-level income, for example, may affect the neighborhood in which one can afford to buy or rent a home.

Both neighborhood SES and HF progression are shown to have a reciprocal association with clinical comorbidities and health behaviors, such as hypertension and smoking. Clinical

comorbidities are not only influenced by ones neighborhood of residence, for example, by the accessibility of healthy foods (Borrell, Diez-Roux, Rose, Catellier, & Clark, 2004), but also may influence whether a person is healthy enough to be employed and can afford to live in a higher SES area (**Figure 3.4**). In addition, there exists evidence that not only can clinical comorbidities exacerbate HF progression, but HF progression may also intensify the severity of clinical comorbidities.

Of particular interest to the current research is the concept of the mechanism of neighborhood SES operating differently on the progression of HF – characterized by rehospitalization, mortality and SRH – among patients with a higher burden of comorbidity. Thus, understanding the role of clinical and social factors in the context of increasing hospitalizations, high mortality rates and declining SRH may help clinicians more optimally treat and manage HF patients and assist public health professionals, communities (O'Dwyer et al., 2007) and organizations to improve prevention efforts and access to care among patients of all levels of neighborhood SES.

Successful interventions to date which have reduced mortality and rehospitalization rates have been multidisciplinary and have included educational modules directed by nurses and other healthcare providers (Hoskins, Walton-Moss, Clark, Schroeder, & Thiel, 1999; Finlay A. McAlister et al., 2004; McDonald et al., 2001; O'Connell, Crawford, & Abrams, 2001; Rich et al., 1995). In a meta-analysis of eight randomized trials, Gwardry-Sridhar (2004) and colleagues found that educational interventions emphasizing medication compliance and lifestyle changes were effective at reducing both mortality and rehospitalization rates, yet acknowledged that existing studies did not provide sufficient follow-up time to quantify the long-term effects of the interventions (Gwadry-Sridhar, Flintoft, Lee, Lee, & Guyatt, 2004).

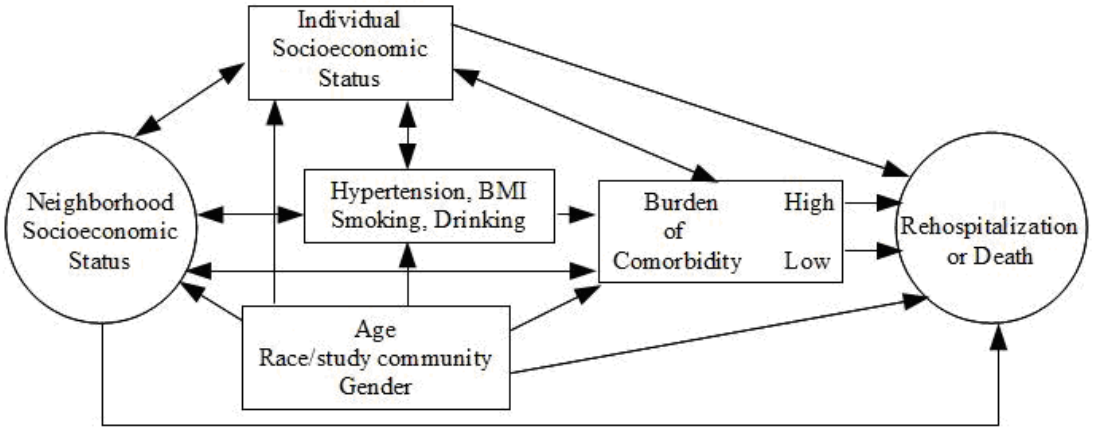
An additional study of 29 randomized trials concluded that patient self-care, follow-up care and access to specialty HF clinics yielded short-term mortality and rehospitalization benefits, but the long-term benefits of such programs remain unknown (Finlay A. McAlister et al., 2004). Moreover, the effects of healthcare interventions may only have benefits in select patient groups. For example, in analyses of ADHERE data (M. Galvao & ADHERE Scientific Advisory Committee (SAC) Investigators, 2005; Marie Galvao et al., 2006), researchers found that while male and female patients had similar in-hospital mortality rates, female patients did not receive the same discharge instructions as men, which may impact longer-term rehospitalization and mortality rates.

Future research, as a response to the current work, may include an assessment of prevention programs and interventions targeted at select neighborhoods based on the neighborhood SES of the area. No published data are available which address whether the neighborhood SES - HF progression relationship differs between patients with and without a high comorbidity burden. If differences in the neighborhood SES - HF progression relationship exist by presence or absence of other chronic diseases, public health professionals may be able to further tailor their prevention messages and interventions to reach the segments of the population at greatest risk of the negative consequences of HF. If certain neighborhoods or patients receiving Medicaid are limited by poor health care quality and access, public health policymakers can play a role in improving HF awareness and standards of care in neighborhood health clinics and providing public access to these outpatient clinics. Also, there may be methodologic implications for future research regarding the refinement of the SRH rubric. Although poor SRH has been shown to be

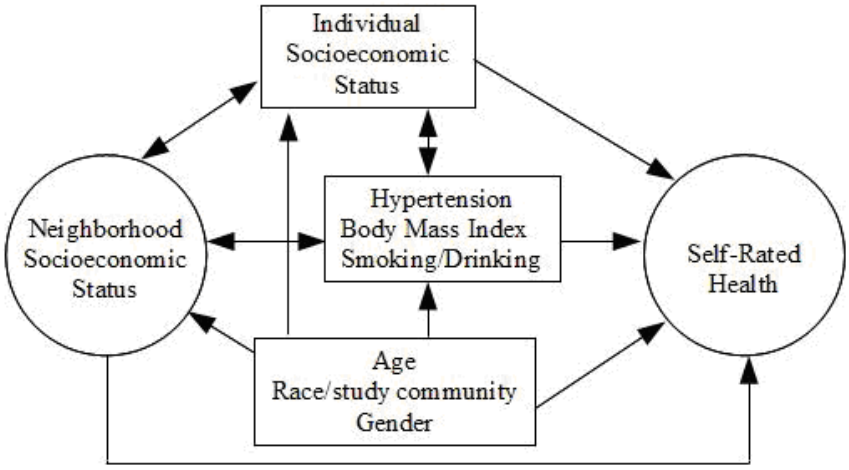
correlated with poor health outcomes, as a result of this research, neighborhood SES information may be investigated as an addition SRH to add to its predictive power.

Figure 3.4. Conceptual models

A. Specific Aims 1 and 2: Rehospitalization or Death.



B. Specific Aim 3: Self-Rated Health.



IV. METHODS

A. Introduction

The objectives of this dissertation were to examine the influence of neighborhood SES and receipt of Medicaid on the progression of HF. The elements of HF progression, rehospitalization, mortality and SRH, represent both incident (death) and repeated (rehospitalization and SRH) outcomes. Also, participants were clustered geographically at the level of the main exposure, the neighborhood. Therefore, the methods for this dissertation required several different approaches for the analysis of multi-level data. The current project involves the analysis of extant data. As such, this section provides a description of the data and the analytic procedures.

B. Atherosclerosis Risk in Communities Study

The ARIC cohort study was designed to investigate the etiology and natural history of atherosclerosis and atherosclerotic disease, and to quantify variation in atherosclerotic risk factors by race, gender, study community, and time. A random selection of approximately 4,000 participants aged 45-64 were recruited from four US communities. At baseline, the ARIC study cohort consisted of 15,792 participants from the following US communities: Forsyth County, North Carolina (NC); Jackson, Mississippi (MS); northwest suburbs of Minneapolis, Minnesota (MN) and Washington County, Maryland (MD). The Jackson, MS sample is comprised solely of African Americans, while the other study communities were

sampled from the entire population of their respective communities (The Atherosclerosis Risk in Communities (ARIC) study: design and objectives, 1989), resulting in an oversampling of blacks in Forsyth County, NC.

The initial visit was conducted in 1987-1989, and re-examinations occurred in 1990-1992 (Visit 2), 1993-1995 (Visit 3), and 1996-1998 (Visit 4). Telephone follow-up is conducted yearly, and used in order to update address, hospitalization, diagnosis, surgery, symptom and medication information. The relationship between visit years, calendar years and telephone contact years (CY) are shown in **Table 4.1**. The shaded cells indicate when in-person visits occurred for each year of enrollment. Medical records are obtained via ARIC surveillance for all hospitalizations occurring after the baseline visit. Discharge diagnoses and cardiovascular event information are recorded by ARIC study abstractors. The cohort is closed, so no additional recruitment or enrollment occurred since baseline.

Table 4.1. Contact years (CY) by year of baseline visit and calendar year, The ARIC study

		Year of Baseline Visit		
Clinic Exam	Calendar Year	1987	1988	1989
	1987	CY 1		
Visit 1	1988	CY 2	CY 1	
	1989	CY 3	CY 2	CY 1
	1990	CY 4	CY 3	CY 2
Visit 2	1991	CY 5	CY 4	CY 3
	1992	CY 6	CY 5	CY 4
	1993	CY 7	CY 6	CY 5
Visit 3	1994	CY 8	CY 7	CY 6
	1995	CY 9	CY 8	CY 7
	1996	CY 10	CY 9	CY 8
Visit 4	1997	CY 11	CY 10	CY 9
	1998	CY 12	CY 11	CY 10
	1999	CY 13	CY 12	CY 11
	2000	CY 14	CY 13	CY 12
	2001	CY 15	CY 14	CY 13
	2002	CY 16	CY 15	CY 14
	2003	CY 17	CY 16	CY 15
	2004	CY 18	CY 17	CY 16
	2005	CY 19	CY 18	CY 17
	2006	CY 20	CY 19	CY 18
	2007	CY 21	CY 20	CY 19

Approximately 1,500 incident hospital admissions for HF occurred among ARIC cohort participants since the baseline examination through December 31, 2004. The current analyses are restricted to African American and Caucasian men and women, aged 45-64 at baseline, with incident hospitalized HF in the ARIC cohort (excluding patients with prevalent HF at baseline, indicated by taking medications for HF in the previous two weeks; or having two of these three symptoms: orthopnea, paroxysmal nocturnal dyspnea or edema in addition

to taking digoxin or diuretics). We considered their respective subsequent hospitalizations, vital status and annual measures of SRH occurring since their incident hospitalized HF event.

1. Socioeconomic Status

US Bureau of the Census data are often used in epidemiologic studies when individual sociodemographic information is unavailable from the medical record (Nancy Krieger et al., 2002). Zip code boundaries are drawn to optimize efficient mail delivery by the US Postal Service. In contrast, census tracts are designed to be socially homogenous (Wen & Christakis, 2005) and are believed to be more representative of the neighborhood context than zip codes (Nancy Krieger et al., 2002). Limitations of the extant research which does include neighborhood SES are: a reliance on zip code boundaries (Rathore et al., 2006) to define neighborhoods, and a lack of access to measures of individual SES in order to determine the independent effect of neighborhood SES on health outcomes.

Neighborhood Socioeconomic Status

Although many researchers use zip code aggregation of neighborhood SES, this practice is mainly one of convenience, as the zip code area may not accurately represent the neighborhood in which an individual resides and conducts activities of daily living. The assignment of geographic areas to zip code boundaries allow for efficient delivery of US mail, while census tracts have an average population size of 4,000 persons and, in contrast to zip codes, are thought to respect political and economic boundaries (Nancy Krieger et al., 2002). Thus, this study utilized neighborhood socioeconomic data assigned to the level of the census tract.

The area-level (neighborhood SES) measure selected for study from the 1990 US Census was median household income (nINC). The 1990 census most closely approximated the timing of the baseline visits for the cohort (1987-1989). In previous work, the use of a single-variable neighborhood SES measure produced results of similar magnitude and precision when compared to a more complex composite index measure of neighborhood SES (Kathryn M. Rose et al., 2009). Participants' addresses obtained at the baseline visit were assigned to the level of the census tract by a vendor with high geocoding accuracy (Whitsel et al., 2004). A previous analysis of mortality in the ARIC cohort reported over 95% of participant addresses at baseline were successfully geocoded to the level of the census tract (Pollitt et al., 2007).

We categorized nINC into community-wide tertiles based upon participants' place of residence at baseline, during the period 1987-1989: low (<$24,777), medium ($24,777≤-<36,071) and high (≥$36,071). All residents living in the study areas during the 1990 US Census contributed to the construction of tertiles of median household income for the current study in order to place the participants' neighborhood income in context with reference to all other residents of the study communities. Each participant in the study sample was assigned the nINC of the census tract in which they resided at baseline. We did not take into account whether or not cohort members changed their address from baseline, as the study population was relatively stable. Unpublished data from the cohort indicate that of participants with complete address information through visit three, 84% had lived in the same census tract since baseline, and even if they changed place of residence, 92% of participants remained in the same nINC tertile throughout follow-up.

Individual Socioeconomic Status

Occupation, income and education are commonly used measures to represent individual SES. ARIC study cohort participants at baseline provided their current or most recent occupation, family income and educational attainment (in years). Current or most recent occupation at baseline was classified into 1980 US Census occupational categories: (1) managerial and professional specialty; (2) technical, sales and administrative support; (3) service; (4) farming, forestry and fishing; (5) precision production, craft and repair; and (6) operators, fabricators and laborers. However, using these categories, 16% of black women and 25% of white women were excluded from an analysis of the relationship between individual SES and atherosclerosis in the ARIC cohort, since their occupation, "homemaker", precluded assignment to a censual category (Diez-Roux, Nieto, Tyroler, Crum, & Szklo, 1995). Since the categorizations of current or most recent occupation are not appropriate for a large number of women in the ARIC cohort, occupation was not used in the current analyses as an individual-level SES variable.

Meanwhile, the classification of annual family income (US dollars) at baseline was as follows: (1) <8,000; (2) 8,000-11,999; (3) 12,000-15,999; (4) 16,000-24,999; (5) 25,000-34,999 and (6) ≥35,000. Income data were missing for 10% or more of black participants, and approximately 5% of white participants at baseline (Diez-Roux et al., 1995). Further, current research suggests that individual-level income is not a preferred indicator of adult SES, since poor health in adulthood may influence one's income potential (Dray-Spira, Gary, & Brancati, 2008). As a result of these findings, we did not use annual family income as an individual-level SES variable in the current analyses.

In contrast, educational attainment data, assessed at baseline among ARIC cohort participants, are complete (Diez-Roux et al., 1995). Educational attainment is categorized among members of the ARIC cohort as: $<8^{th}$ grade; $8^{th} – 11^{th}$ grade; high school or general equivalence diploma (GED); some vocational school; 1 – 3 years of college; 4 years of college completed and some graduate or professional school (Borrell et al., 2004). In the current study, we characterized education as (1) less than high school; (2) high school or GED or (3) greater than high school. According to previous research done in the ARIC cohort, these three educational levels appear to warrant their own categories, and should not be dichotomized, for example, at the level of high school education (Diez-Roux et al., 1995), as approximately 40% of participants had less than a high school education and 35% were high school graduates or had their GED at study baseline.

Several investigators use insurance status as a surrogate for individual SES (Ayanian et al., 1993; Harnick, Cohen, Schechter, Fuster, & Smith, 1998; Shen, Wan, & Perlin, 2001), although the validity of this approach is unknown. Insurance status is available in ARIC from the incident HF hospitalization medical record, and is defined as follows: Prepaid health insurance (health maintenance organization [HMO] or private insurance), Medicare, Medicaid, and other types of insurance (e.g., governmental insurance or workers' compensation). Receipt of Medicaid (yes/no) was used in this analysis, as indicated in the medical record. Medicaid coverage may be a reasonable proxy for low individual SES, as the majority of Medicaid beneficiaries also have incomes below the poverty line (Ku, 2005). Previous work in ARIC surveillance indicates that receipt of Medicaid may influence care-seeking behavior (Foraker et al., 2008).

2. Incident Hospitalized Heart Failure

Hospitalization data in the ARIC cohort are collected via the Cohort Event Eligibility (CEL) form (ARIC, 2007a). A CEL form is completed for a cohort participant by ARIC study personnel if a hospitalization is identified: (1) during the annual follow-up (AFU) telephone contact; (2) via ongoing ARIC community surveillance; or (3) while investigating an unrelated hospital admission of the cohort participant. The target date for AFU contacts is the one-year anniversary of the first clinic visit for each participant. Cohort participants are followed-up each year thereafter by telephone in order to maintain correct address information, and to document vital status and medical events (e.g., hospitalizations, surgeries, medications) occurring since the last contact.

Trained staff conduct telephone interviews and complete an AFU form (ARIC, 2008) for each participant. Participants are contacted yearly, regardless of whether or not they continue to reside within ARIC study boundaries. Since the inception of ARIC, information regarding overnight (i.e., inpatient) hospital stays has been collected as part of the AFU. Recent versions of the AFU (specifically, forms L and M) also ascertained outpatient hospital admissions, however, those data were not yet available at the time of this investigation and thus were not incorporated into the current analyses. Administratively, the AFU and CEL forms must be linked in order to make certain all overnight hospitalizations ascertained via the AFU are investigated.

Inpatient hospitalization data is abstracted from the medical record and recorded on the CEL if the hospital is within the ARIC study boundaries and the records are complete, or if the hospital is located outside of the catchment area and the medical record can be obtained.

Thus, the CEL form can be used to track each hospitalization for every cohort member since baseline. Data contained in the CEL form include, but are not limited to, the date of discharge or death and ICD-9-CM discharge codes recorded in the order listed on the hospital discharge index.

All-cause hospitalizations are identified during annual follow-up or during routine ARIC surveillance (White et al., 1996). For the purpose of this study, cardiovascular disease (CVD)-related hospitalizations were further identified from all-cause hospitalizations using ICD-9-CM discharge codes *402*, *410-414*, *427*, *428*, *430-436* or *518.4*; while a HF-related hospitalization was defined as that with an ICD-9-CM discharge code *428* (ARIC, 2007a).

If the ICD-9-CM discharge codes or terms used in the discharge summary reference a CVD-, stroke, or HF-related hospitalization, then an appropriate hospital data abstraction form is completed for that hospitalization (ARIC, 2007d). Hospital data abstraction forms contain information on co-occurring illnesses and clinical comorbidities, as well as procedures performed during the hospital stay.

3. Progression of Heart Failure

For the purposes of this work, progression of HF following an incident hospitalized event was defined in three domains: rehospitalization, mortality and SRH.

i. Rehospitalizations

Hospitalizations are routinely assessed in ARIC as previously described. Briefly, as part of annual follow-up, information regarding inpatient hospital stays is collected, and

hospitalization data are abstracted from the medical record regardless of the location of the hospital. All-cause hospitalizations, in addition to CVD- and HF-related hospitalizations, were ascertained for members of the cohort following their incident hospitalized HF event.

ii. Mortality

Mortality data in the ARIC cohort are collected via the CEL form and AFU. Mortality data contained in the CEL form come from death certificates and provide the date, cause of death, and whether the death occurs in-hospital. For the purpose of these analyses, cause of death will not be used due to a primary interest in all-cause mortality and the anticipated limitations of cause of death data. In ARIC, CEL and AFU mortality data are supplemented by informant interview, witness reports, physician questionnaires and autopsy reports, if applicable. In addition, National Death Index searches are conducted annually to account for any cohort members whose vital status is not known through the AFU contact attempt.

Mortality was measured by ascertainment of deaths occurring within 30-, 60-, and 90 days, and one year and five years, respectively, of the incident hospitalized HF event. The date of all deaths were located in CEL data and were classified as within 30-, 60-, or 90 days, one year or five years of the incident hospitalized HF event (yes/no). Approximately half of all ARIC cohort participants with incident hospitalized HF were deceased by December 31, 2004.

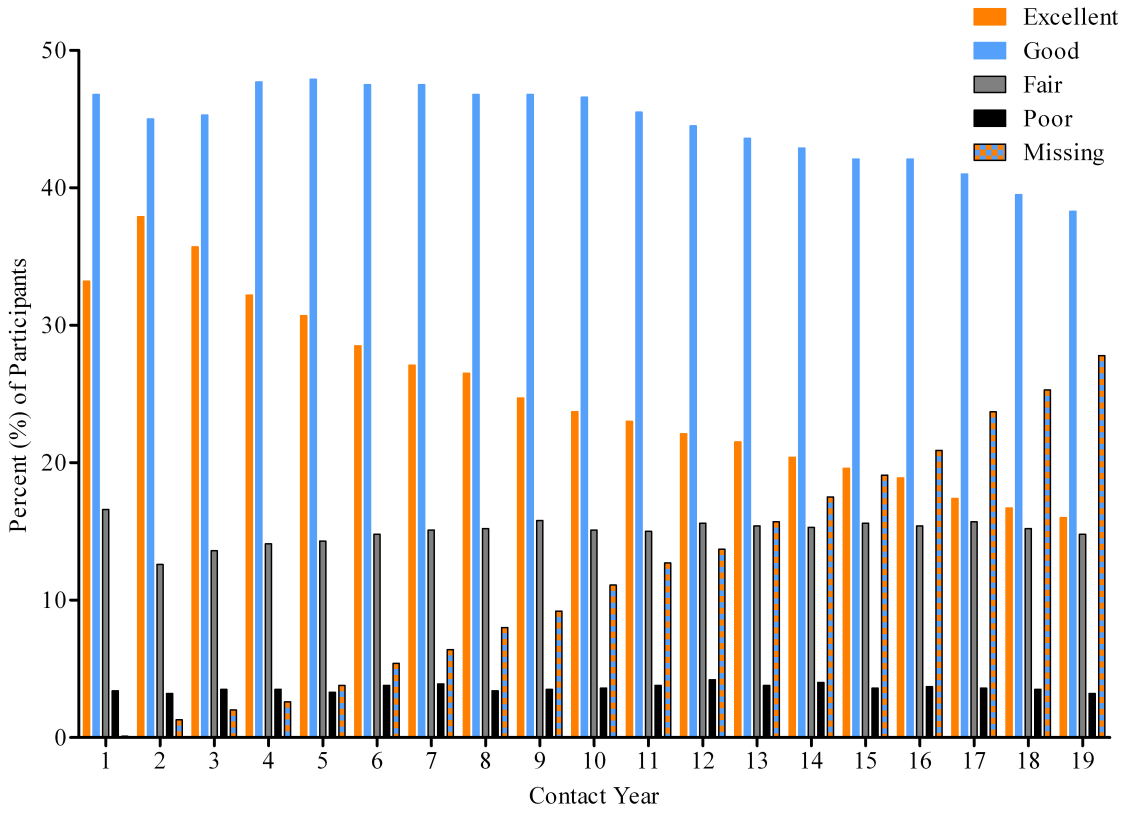
iii. Self-rated Health

SRH is thought to reflect both mental and physical health domains, and is assessed by asking individuals to objectively describe their health status. SRH is associated with disease

incidence and subsequent mortality. SRH was measured at baseline and at each AFU with the question, "Over the past year, compared to other people your age, would you say that your health has been *excellent*, *good*, *fair* or *poor*?" To get an accurate picture of SRH, however, it is important to take death into consideration in analyses. For example, if only live participants are considered during follow-up, SRH may be shown to improve after a sentinel health event, since the sickest patients (i.e., those with *fair* or *poor* SRH) have died (Paula Diehr & Patrick, 2003).

Figure 4.1 shows reported SRH across all contact years of follow-up among members of the ARIC cohort. In increasing follow-up years, we see a steady decline in the percent of participants reporting *excellent* health while the proportion of participants reporting *good* health remains relatively consistent over time. Meanwhile, the percent of participants reporting *fair* health increases slightly over time, while the proportion of participants reporting *poor* health does not vary over time. It is of note that ascertainment of the SRH measure is nearly complete for early follow-up years, however, the results shown in **Figure 4.1** are based on fewer cohort members as follow-up progresses and the amount of *missing* data due to death and – nearly negligible – loss to follow-up increases over time.

Figure 4.1. Reported self-rated health across all contact years, The ARIC study



A SRH response set is not precisely ordinal, therefore, we transformed the SRH responses according to Diehr et al. (Paula Diehr et al., 2005): 95 for *excellent*, 80 for *good*, 30 for *fair*, 15 for *poor*, and 0 for *death*. This transformation represents the estimated probability of persons being healthy two years later, as developed from several data sources, including the Cardiovascular Health Study (Paula Diehr & Patrick, 2003; P. Diehr et al., 2001). In addition, the ARIC cohort had experienced little loss to follow-up, therefore, were able to estimate (i.e., interpolate) missing SRH data, with the exception of data missing due to death, from data collected before and after the missing SRH assessment. If a cohort member died during follow-up and was not contacted for annual follow-up the year of their death, they were assigned a SRH value of zero for that year and each year thereafter.

4. Covariates

All statistical modeling approaches involved the assessment of confounding and effect measure modification. Effect measure modification (EMM) was investigated using a $p<0.2$ level of significance for the outcomes of rehospitalization or death. Meanwhile, a <0.05 level of significance for EMM was used for the outcome of SRH, as the large sample size due to yearly measures of SRH provided more power to detect effect measure modification. For all analyses, a variable must have been statistically significantly ($p<0.05$) associated with both the exposure and the outcome to be considered a potential confounder. Confounding was assessed using a 10% change in estimate strategy (McNamee, 2003). Variables appearing in **Table 4.2** were first assessed using a Directed Acyclic Graph (DAG) to determine whether these potential confounders met the following confounding criteria: (1) the covariate was associated with HF progression; (2) the covariate was associated with neighborhood SES and (3) the covariate was not affected by neighborhood SES (Rothman, 2002).

Table 4.2. Selected covariates and the assessment of effect measure modification and confounding, The ARIC study

Exposure: nSES	**Outcome: HF Progression**
Tertiles (low-, medium-, high-) of US census-tract median household income	Rehospitalization and death Self-rated health
Potential Confounders*	**Potential EMMs**
Age	Comorbidity score
Race / study community	Hypertension
Gender	Overweight / obesity
Education	Smoking status
Medicaid status	Alcohol use

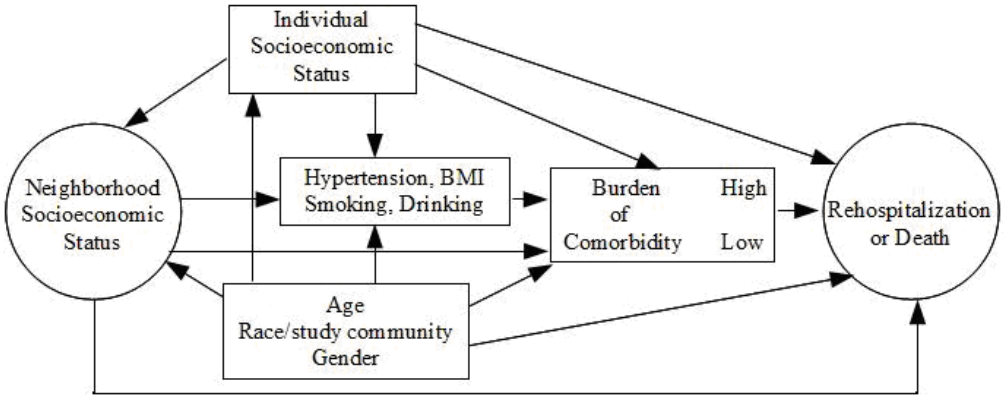
*Potential confounders will first be explored as potential effect modifiers

Plausible causal relationships were indicated in the DAGs (**Figure 4.2**) by unidirectional arrows. Acyclic relationships are one feature which differentiates the DAGs shown in

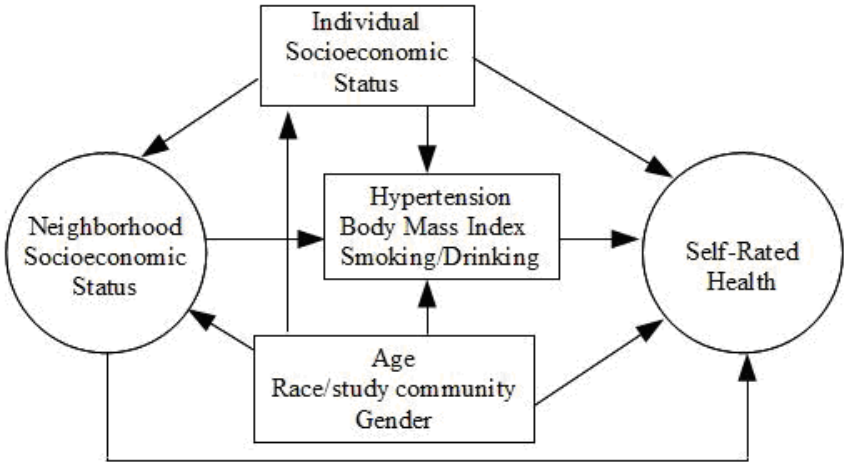
Figure 4.2 from the conceptual model shown in **Figure 3.4**. When constructing a DAG, it was up to the researcher to decide, based on extant literature and biologic plausibility, whether, for example, neighborhood SES was more likely to "cause" clinical comorbidity, or if clinical comorbidity was more likely to "cause" neighborhood SES. In the current study, the exposure preceded the diagnosis of HF and the subsequent progression of the disease. Thus, it was unlikely that the disease, or even precursors to the disease, affected the neighborhood in which the participants resided at baseline. Therefore, the unidirectional arrow originates from neighborhood SES and points toward clinical comorbidity (**Figure 4.2**).

Figure 4.2. Directed acyclic graphs with all unidirectional arrows

A. Specific Aims 1 and 2: Rehospitalization or Death.



B. Specific Aim 3: Self-Rated Health.



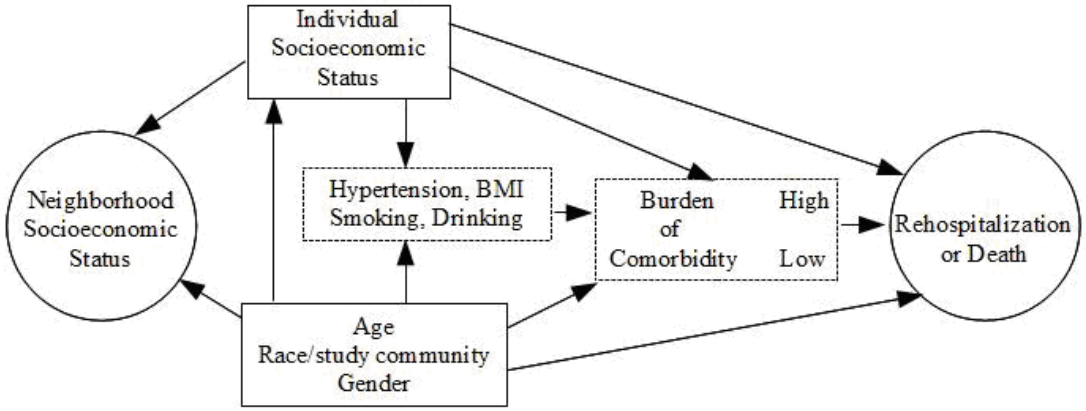
In order to fulfill the criteria as a potential confounder, variables in the DAG must: (1) have an arrow pointing in either direction between them and HF progression; and (2) have an arrow pointing from them to neighborhood SES. Variables such as clinical comorbidity and health behaviors have arrows pointing to them from neighborhood SES, and thus have the potential to be on the causal pathway between neighborhood SES and HF progression. Caution should be taken before adjusting for variables along the causal pathway, as doing so may create bias (Jager, Zoccali, MacLeod, & Dekker, 2007). All potential confounders of the neighborhood SES and HF progression relationship were first considered as effect measure modifiers and then as potential confounders.

As **Figure 4.3** shows, once the arrows pointing from the exposure, neighborhood SES, are removed, unblocked backdoor paths exist via demographic variables and individual SES. Thus, demographic variables and individual SES are potential confounders, and according to the DAG shown in **Figure 4.3**, once they are controlled for in the analysis, the paths from

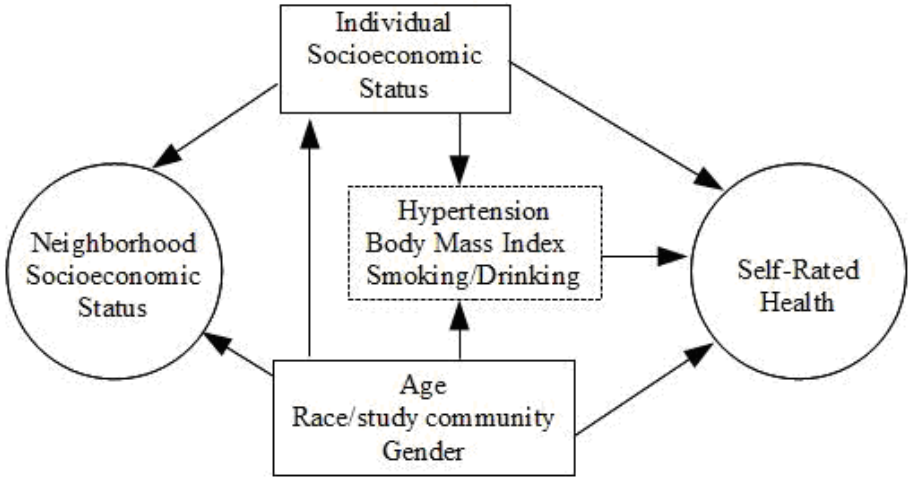
neighborhood SES to HF progression leading through clinical comorbidities and health behaviors are blocked.

Figure 4.3. Directed acyclic graphs without unidirectional arrows eminating from exposure

A. Specific Aims 1 and 2: Rehospitalization or Death.



B. Specific Aim 3: Self-Rated Health.



Covariates included race/study community, gender, age and selected socioeconomic, clinical and behavioral characteristics.

Sociodemographic Characteristics

In the study of rehospitalization and mortality, we determined participants' age on the date of the incident HF hospitalization. For the SRH analyses, we incorporated age at the time of the AFU contact. In order to conserve power, we treated age as a continuous variable, centered at the mean. The analyses included males and females, and we constructed composite variables for self-reported race (black/white) and ARIC study community [Forsyth County (Co.), NC; Jackson, MS; northwest suburbs of Minneapolis, MN; and Washington Co., MD] into the following categories: black/Forsyth, white/Forsyth Co., black/Jackson, white/Minneapolis, white/Washington Co.

Socioeconomic Characteristics

Occupation, income and education are commonly used measures to represent individual SES. ARIC study cohort participants at baseline provided their current or most recent occupation, family income and educational attainment (in years). Educational attainment was assessed at baseline (less than 11 years, high school graduate, and greater than high school), as was health insurance status at the time of the index HF hospitalization (receipt of Medicaid, yes/no).

Clinical and Behavioral Characteristics

Blood pressure was measured at study visits one through four with random-zero mercury manometers per ARIC study protocol (ARIC, 1988). Hypertension was defined at

baseline by either a (1) systolic blood pressure ≥140 mmHg; (2) diastolic blood pressure ≥90 mmHg or (3) recent history of antihypertensive medication use. For the purpose of these analyses, the highest of the blood pressure measures or an indication of antihypertensive medication taken at the time of the baseline visit was used to represent the participant's hypertensive status. Loehr et al. report a hypertension prevalence of 52% at baseline among incident HF participants ascertained through 2004 in the ARIC cohort (Loehr et al., 2008).

Height and weight were measured at each clinic visit by technicians per ARIC study protocol (ARIC, 1988). Briefly, height and weight were measured with participants in scrub attire following an overnight fast. Height was measured using a wall mounted ruler, and weight was measured on a scale which was zeroed and calibrated per study protocol (Loehr et al., 2009). We calculated BMI (weight in kilograms [kg]/height in meters squared [m^2]) from these data points. For the purpose of these analyses, the highest of the measures taken at baseline were used to represent the participant's BMI. BMI was categorized as normal weight (<25 kg/m^2), overweight (≥25 to <30 kg/m^2), or obese (≥30 kg/m^2) (Loehr et al., 2008; NIH, 1998). According to baseline data from ARIC through 2004, participants with incident HF averaged a BMI of 29.7 kg/m^2 (standard deviation 6.2 kg/m^2) (Loehr et al., 2008).

Current smoking and current drinking (yes/no) were assessed at study baseline.

Comorbidity Index Score

Patients diagnosed with HF often have coexisting clinical comorbidities. Chronic conditions such as hypertension, CHD, diabetes and obesity are risk factors for the development of HF (Schocken et al., 2008; Weir et al., 2006), and clinical HF is commonly

accompanied by one or more of these factors (Heywood et al., 2007). In general, the burden of mortality (Charlson et al., 1987; Deyo et al., 1992; Jong et al., 2002) and rehospitalization (Philbin & DiSalvo, 1999) increases with increasing comorbidity.

The effect of neighborhood SES may act through risk factors for CVD, as certain conditions are believed to be more common in low neighborhood SES areas (Stjarne et al., 2006). Therefore, there exists evidence that comorbid conditions are on the causal pathway between neighborhood SES and HF progression (**Figure 4.3**).

The Charlson index of comorbidity was originally developed using comorbid conditions present among breast cancer patients and validated on a sample of consecutive New York Medical Center patients (Charlson et al., 1987). Charlson et al. (1987) first assessed the effect of an absolute number of comorbid illnesses on mortality, and then transformed the list of comorbid illnesses to include a numeric score which accounted for the seriousness of each comorbid illness. Deyo et al. translated the Charlson index into a list of ICD-9-CM discharge codes for use with administrative databases (Deyo et al., 1992). In general, each one-point increase in index score results in a dose-response increase in mortality, length of stay, surgical complications and hospital charges (Charlson et al., 1987; Deyo et al., 1992).

For the rehospitalization and mortality analyses, we ascertained the prevalence of common underlying conditions at the time of the index HF hospitalization using ICD-9-CM discharge codes. The Charlson index, a clinical comorbidity algorithm (Deyo et al., 1992), was derived from these data (**Table 3.2**).

The sum of all of the discharge-code related score values (**Table 3.2**) results in a total index score for each patient. A cutpoint of three points has been previously used in the

literature to define those with a high burden of comorbidity (three or more points) from those with a low burden of comorbidity (two or fewer points) (Charlson et al., 1987; Deyo et al., 1992). In its use with HF outcomes, a "modified" Charlson index excludes chronic HF from the conditions included in the computation of the comorbidity score (Senni et al., 2006). Consistent with previous studies including participants with chronic HF, we defined a high burden of comorbidity as a sum of two or more points on the Charlson index scale, whereas a low burden of comorbidity was defined with a total of less than two points.

C. Aim 1: Analyses

After excluding 245 participants with prevalent HF at baseline, 1,415 participants had an incident hospitalized HF event during follow-up (1987-2004). An additional 70 participants were excluded due to missing data on neighborhood SES, and 3 were excluded because they were not white or black, or were blacks living in Minnesota or Maryland, resulting in a final sample size of 1,342 participants.

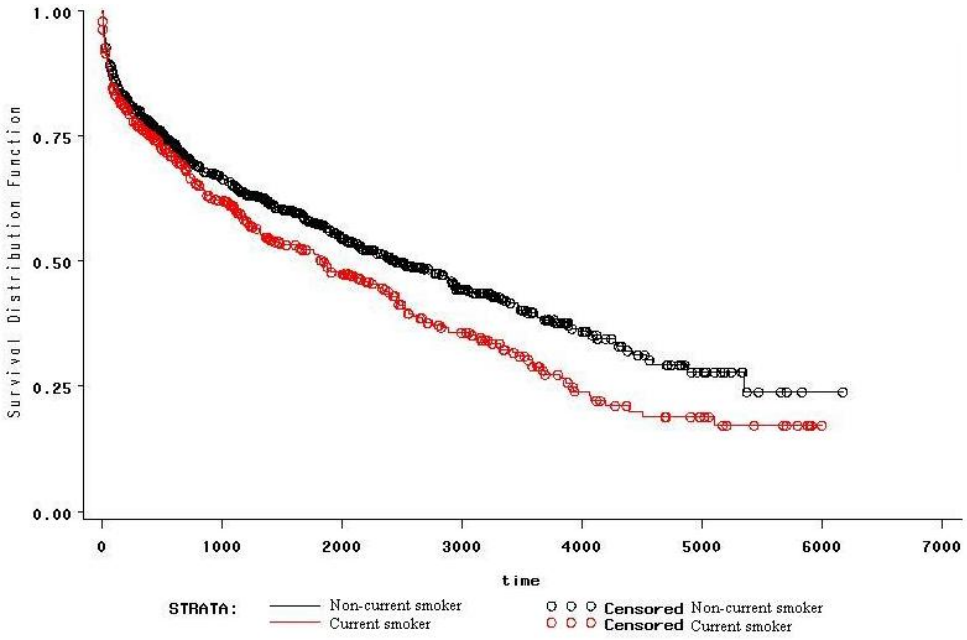
Time to first hospital readmission (all-cause, CVD- and HF-related rehospitalization) was an outcome of interest for this analysis. We also examined the rate of readmission (total number of rehospitalizations over person-time of follow-up) for all-cause, CVD-related and HF rehospitalizations. We conducted both time-to-event analyses as well as logistic regression to assess the risk of 30-day, 1-year and 5-year rehospitalization.

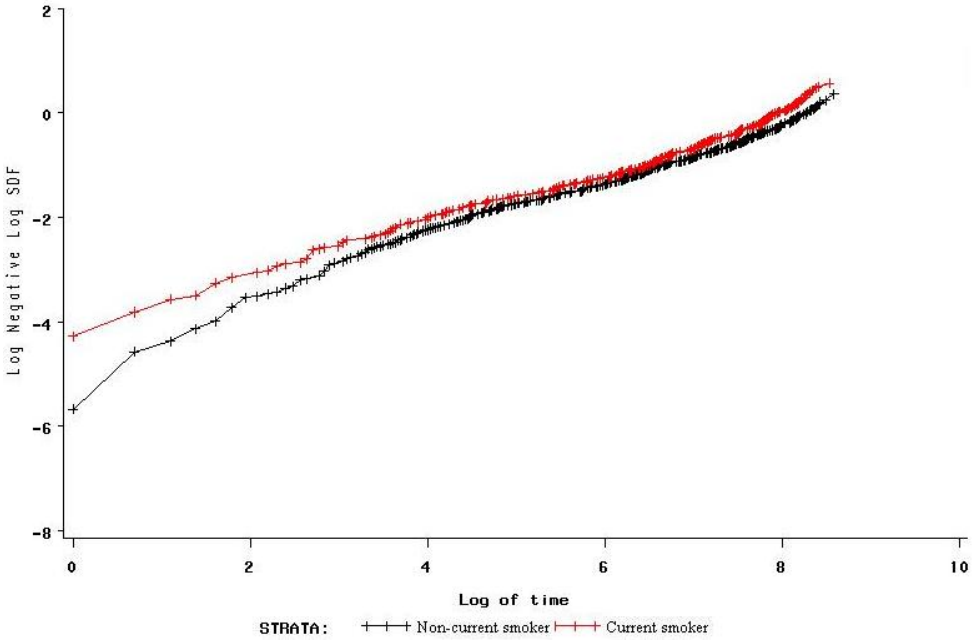
Crude nINC-rehospitalization analyses were conducted, the influence of covariates in a full model were tested, and effect modification ($p_{interaction}<0.05$) of the nINC-rehospitalization relationship was assessed by age, race/study community, gender, hypertension, BMI, smoking, drinking and comorbidity index score.

1. Time to Rehospitalization

We measured time to readmission over the course of follow-up since the incident hospitalized HF event by the product-limit (Kaplan-Meier) method (Cox, 1972; Symons & Moore, 2002). An assumption of survival analysis is that the distribution of survival free of hospitalization for those who are censored (i.e., who died or were lost to follow-up) would have been the same as the non-censored had they not been censored. Also, the model assumes that events are independent. The model produced survival curves depicting survival free of readmission. The proportional hazards (PH) assumption was examined for every variable in the model, both graphically using survival probability and log (-log) survival plots (**Figure 4.4**) and with hypothesis tests evaluating time interaction terms. In both types of plots, parallel lines indicate the PH assumption is not violated. The PH model is non-parametric, and thus allows for flexibility of assumptions.

Figure 4.4. Survival probability and log (-log) survival plots of current smoking





PH regression was conducted to quantify time elapsed between the incident HF hospitalization and the first rehospitalization. Hazard ratios were estimated comparing categorical levels of neighborhood SES in crude and multivariable models. In the multivariable models, ties were handled with the Efron method. Incident HF hospitalizations which resulted in death were censored at the time of death, as those patients were no longer eligible for rehospitalization at that time. Multivariate Cox proportional hazard models estimated the risk of rehospitalization using death during follow-up as a censoring variable. All participants were censored at the end of 2004.

2. Rehospitalization Rate

We used SAS software (SAS Institute, Cary, NC) with the procedure PHREG and the repeated events option to model rehospitalization rates, accounting for the clustering of events within patients and patients within geographic area while investigating all-cause,

CVD-related and HF-related hospitalization rates, respectively. Time at risk for rehospitalization was the time elapsed between the incident HF hospitalization admission date until rehospitalization, death, loss to follow-up or the end of 2004, whichever came first. The rate was calculated as the number of hospitalizations per participant over the person-time at risk for the participant. The hospitalization count was modeled with the logarithm of person-days at risk as the offset.

All-cause hospitalizations were identified during annual follow-up or during routine ARIC community surveillance (White et al., 1996). For the purpose of this study, CVD-related hospitalizations were further identified from all-cause hospitalizations using ICD-9-CM discharge codes *402*, *410-414*, *427*, *428*, *430-436* or *518.4*; while a HF-related hospitalization was defined as that with an ICD-9-CM discharge code *428* (ARIC, 2007a).

We used generalized linear Poisson mixed models to estimate rehospitalization rate ratios, comparing the rehospitalization rates of participants from low nINC to high nINC and from medium nINC to high nINC, along with 95% confidence intervals (RR, 95% CI). The assumptions of the Poisson model are that events are independent and the probability of an event occurring within an interval is proportional to the length of the interval. Standard Poisson variance assumptions were verified by testing for over-dispersion (Dallal, 2008; Rao & Scott, 1999), and we calculated robust variance estimates accordingly.

Over-dispersion

We used Poisson regression to model the natural log of the expected count of hospitalizations per unit time post-incident HF event, using the natural logarithm of the follow-up time as the offset. A potential limitation of the Poisson distribution is that it may

not be able to predict the underlying distribution of count data per unit time in the source population. When the data are more variable than the distribution assumed by the Poisson model, the data are said to be overdispersed.

In the case of our rehospitalization data, it was possible that more patients than expected were not rehospitalized, that is, experienced a count of zero for the number of rehospitalizations per unit time. There are several statistical techniques used to assess over-dispersion in a Poisson distribution. We fitted a Poisson regression model to the data, as previously described, using the natural logarithm of person-time as the offset. We consulted the deviance statistic (Dallal, 2008) to determine if the ratio was close to one. Over-dispersion is indicated by the deviance statistic (divided by its degrees of freedom) if the ratio is greater than one.

Given a deviance statistic greater than one, we fitted negative binomial regression to the rehospitalization data, using the natural logarithm of person-time as the offset. Again, the deviance statistic was consulted. If the negative binomial regression model fit the underlying data distribution more effectively, the deviance statistic would be closer to one. In the comparison of the Poisson and negative binomial models, we expected to find similar effect estimates from both models, however, due to a review of the literature comparing the two modeling strategies, we anticipated the width of the 95% CIs would be larger when using the negative binomial model (Dallal, 2008), as the model estimates derived from overdispersed data are not as precise as the Poisson model may indicate.

In our data, the Poisson models yielded a deviance statistic of close to four. Thus, over-dispersion was suggested. In response, we fit negative binomial models to the data and

observed deviance statistics just below 1.2. As expected, the point estimates of the rate ratios did not change. However, the 95% CIs widened considerably with the application of the negative binomial model. The imprecision of the estimates reflect the effect over-dispersion has on these data. Estimates and 95% CIs from the negative binomial models are shown in the **Appendix**. Although the estimates were less precise, the supplemental analyses accounting for over-dispersion did not change our interpretation of the results.

3. Risk of Rehospitalization

We performed logistic regression to estimate the risk of 30-day, one-year and five-year rehospitalization. Neighborhood SES and other covariates were assessed for linearity in the logit. Logistic regression (PROC LOGISTIC, SAS Version 9.1, Cary, NC) was used to assess the influence of neighborhood SES on 30-day, one-year and five-year rehospitalization among HF patients in crude and multivariable models.

D. Aim 2: Analyses

Time to death was an outcome of interest for this analysis. We conducted time-to-event analyses as well as logistic regression to assess the risk of 30-day, one-year and five-year mortality. Crude nINC-mortality analyses were conducted, the influence of covariates in a full model were tested, and effect modification ($p_{interaction}<0.05$) of the nINC-mortality relationship was assessed by age, race/study community, gender, hypertension, BMI, smoking, drinking and comorbidity index score.

1. Time to Death

We measured time to death over the course of follow-up since the incident hospitalized HF event by the product-limit (Kaplan-Meier) method (Cox, 1972; Symons & Moore, 2002). An assumption of survival analysis is that the distribution of survival for those who are censored (i.e., who died or were lost to follow-up) would have been the same as the non-censored had they not been censored. Also, the model assumes that events (deaths) are independent. The model produced survival curves depicting survival since the incident HF hospitalization. The proportional hazards (PH) assumption was examined for every variable in the model, both graphically using log (-log) survival plots (**Figure 4.4**) and with hypothesis tests evaluating time interaction terms. The PH model is non-parametric, and thus allows for flexibility of assumptions.

PH regression was conducted to quantify time elapsed between the incident HF hospitalization and mortality. Hazard ratios were estimated comparing categorical levels of neighborhood SES in crude and multivariable models. In the multivariable models, ties were handled with the Efron method. Multivariate Cox proportional hazard models estimated the risk of death during follow-up without competing risk. All participants were censored at the end of 2004.

i. Combined Endpoint: Rehospitalization or Death

A combined endpoint of rehospitalization or death was also explored in these analyses. We conducted time-to-event analyses for rehospitalization or death, whichever came first, as well as logistic regression to assess the risk of 30-day, 1-year and 5-year rehospitalization or death. Crude nINC-rehospitalization/mortality analyses were conducted, the influence of

covariates in a full model were tested, and effect modification ($p_{interaction}<0.05$) of the nINC-rehospitalization/mortality relationship was assessed by age, race/study community, gender, hypertension, BMI, smoking, drinking and comorbidity index score.

2. Risk of Death

The date of all deaths were located from annual follow-up (AFU) data and were classified as within 30 days, one-year or five years of the incident hospitalized HF event (yes/no). Neighborhood SES and other covariates were assessed for linearity in the logit. Logistic regression (PROC LOGISTIC, SAS Version 9.1, Cary, NC) was used to assess the influence of neighborhood SES on 30-day, one-year and five-year mortality among HF patients in crude and multivariable models. Low SES-to high SES and medium SES-to high SES risk ratios for mortality were estimated using logistic regression.

E. Aim 3: Analyses

ARIC study staff conducts annual follow-up by telephone to update address and contact information, and to assess overnight hospitalizations and changes in health status occurring since the last annual contact. SRH was measured among 15,792 black and white men and women at baseline and at each annual follow-up (1987-2006) for a median of 17.6 (range 1-19) years using the question, "Over the past year, compared to other people your age, would you say that your health has been *excellent*, *good*, *fair* or *poor*?" We transformed these responses to represent the estimated probability of being healthy in the future based on their current response (Paula Diehr et al., 2005): 95 for *excellent*, 80 for *good*, 30 for *fair*, 15 for *poor*, and 0 for *death*.

Participants' baseline place of residence (1987-1989) was geocoded to the level of the census tract by a vendor with demonstrated accuracy, as described elsewhere (Whitsel et al., 2004). Neighborhood-level median household income (nINC) was obtained from the 1990 US Census and averaged across all ARIC study communities. Participants were assigned a tertile of nINC [low (<$24,777), medium ($24,777≤-<36,071) or high (≥$36,071)] based upon their address at baseline.

There were 276,200 total SRH observations for members of the cohort, of which 9,552 (3.4%) were missing. If an observation was missing, and there were complete SRH values for both the previous and subsequent year of follow-up, we imputed the missing observation by averaging the values from the previous and subsequent years. As a result, over half (N=5,140) of the missing observations were imputed. We assigned a zero for the missing value if it occurred during the year in which the cohort member died. In order to capture the SRH of the entire cohort across time, and not just that of the survivors, we included observations through contact year 19 for members lost to follow-up or who were deceased, and assigned a zero for each follow-up year which occurred after the cohort members' death.

Of the original 15,792 cohort members, 754 were excluded due to missing nINC (N=13,030 SRH observations), resulting in 263,170 SRH observations available for these analyses. We analyzed mean SRH at discrete time points and trajectories of SRH across time among participants who were disease-free at baseline and disease-free throughout follow-up (N=11,188), as well as among those receiving a diagnosis of incident myocardial infarction (MI; N=1,071), any stroke (N=809), heart failure (HF; N=1,592) or lung cancer (N=433), and those undergoing cardiac revascularization procedures (N=1,340) during follow-up. Cardiac procedures were defined as operations on the vessels of the heart, including bypass

and revascularization (ICD-9-CM *36.0*, *36.1* and *36.2*). We assessed SRH data through the end of 2006, and incident events through the end of 2005, in order to give each cohort member at least one year of follow-up post-event.

For comparison purposes, each member of the disease-free group was assigned a random "event" date (P. Diehr et al., 2001). As a result, the pre-event and post-event trajectories from the incident disease groups could be compared to those of the group which remained healthy throughout follow-up, to determine if the SRH trajectories among the diseased differ from the trajectory of SRH that would be expected due to disease-free aging. With regard to differences by incident disease status, HF survival has been shown to be worse than other cardiovascular diseases and cancers, with the exception of lung cancer (Simon Stewart et al., 2001), and it remains unknown if SRH trajectories show similar trends.

Factors influencing pre- and post-event trajectories were of interest, as well as covariates which played a role in the decline of SRH over the follow-up period. Age (centered at 65 years) and age squared at the time of the annual follow-up contact were included in statistical models. Gender and race/study community were the additional demographic variables of interest. Health status and behavior variables assessed at baseline included body mass index (BMI), classified into normal (referent, <25 kg/m^2), overweight (25-<29.9 kg/m^2) or obese (≥ 29.9 kg/m^2); hypertension, present if systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or if taking hypertensive medication within the previous two weeks; current drinker and current smoker. Educational attainment was assessed at baseline and categorized as less than 11 years, high school graduate, and greater than high school (referent). We accounted for period effects [1987-1992 (referent), 1993-1999 and 2000-2006] at each annual follow-up contact in order to capture secular trends (Rice, Lang,

Henley, & Melzer, 2010) which may influence the nINC-SRH relationship, such as changes in health behaviors and disease treatments occurring in the ARIC communities over time.

Repeated assessments of SRH were accounted for using individual quadratic growth models. McCullough and Laurenceau used a similar modeling strategy in their analysis of the natural history of SRH (McCullough & Laurenceau, 2004). Specifically, SRH for each participant was regressed on age for pre-event, post-event, entire follow-up, and at each time point of interest (e.g., three, two and one year prior, as well as the event year and one, two, three, four and five years after the event). The y-intercept was then the mean (centered at 65) age of participants at the time of the AFU contact. The standard equation assumed a linear pattern of growth or decline. As such, we also computed a quadratic model and a cubic model to assess for the best fit to the data.

After choosing a quadratic model by way of comparing deviance statistics, we regressed individual differences in estimated SRH on between-participant differences in neighborhood SES, gender and race/study community, health behavior and clinical variables collected at baseline (McCullough & Laurenceau, 2004). The main relationship of interest in these analyses was that between levels of neighborhood SES and SRH. We expected to see a steeper decline in mean SRH among participants living in low neighborhood SES areas compared to high neighborhood SES areas.

We also regressed incident disease-specific SRH at each time point of interest (e.g., baseline; three, two, and one year prior to the event; event year; and one, two, three, four and five years post-event) on study covariates to generate estimated adjusted SRH values and standard errors (PROC GLM, SAS 9.1.3, Cary, NC). We used the change in adjusted SRH

between the year of event and one year later to calculate how much of the decline in SRH post-event was due to death for each incident disease group. For example, we calculated the mean adjusted decline in SRH among participants who were alive one-year post event and divided that value by the mean adjusted decline in SRH among all participants (regardless of vital status). The proportion of decline in SRH post-event due to deaths was then one minus the aforementioned value.

If a relationship between nINC and SRH exists, it is feasible that nINC may influence the slope of decline in SRH over time depending on the type of incident health condition. Thus, we fit individual quadratic growth models separately to data by incident disease group, accounting for repeated measures of SRH (PROC MIXED, SAS 9.1.3, Cary, NC). Effect measure modification of the nINC-SRH relationship was assessed (disease-free: $p_{interaction}<0.01$; other disease: $p_{interaction}<0.05$) by demographic, medical history and health behavior variables.

1. Alternative Approach

In 2001, the procedure "TRAJ" was developed by Jones et al. for SAS statistical software in order to analyze developmental trajectories (Clark, Jones, Wood, & Cornelius, 2006; Jones & Nagin, 2007). We explored its potential for analyzing trajectories of SRH over time among members of the ARIC cohort. Its appeal was the incorporation of both mixed and latent growth curve modeling. Thus, this technique accounts for repeated measures of SRH among participants, and is designed to allow for individual variations in trajectories over time. Specifically, the censored normal (CNORM) model had previously

been used with psychometric measure data (Jones & Nagin, 2007), and had the potential to be applied to our continuous SRH data.

Our repeated measures SRH data were structured in a long format, with rows of observations representing each contact year within participants. For use with the TRAJ procedure, the data were transformed to the wide format, with one row of observations per participant and columns representing each contact year. We downloaded the TRAJ module compatible with SAS Version 9.x, which is available from the developer's website (Jones, 2010). The TRAJ procedure identifies different parameter values in the data and utilizes the information to group the data into a specified number of groups.

The TRAJ procedure does not allow the researcher to specify the type of groups or the parameters by which the groups should be created. It is the purpose the TRAJ procedure to identify salient groups from the data given. Therefore, the TRAJ procedure is beneficial to researchers who wish to identify distinct groupings within their data. For example, the TRAJ procedure can identify distinct subpopulations, or components of the data which can in turn predict group membership. Another benefit of the TRAJ procedure, in addition to its ability to handle repeated measures data, is that it can accommodate time-varying covariates.

The goal of our work was to define the groupings for our data *a priori*. For example, an aim of the current work was to determine if the trajectories of SRH over time differed by neighborhood SES in the ARIC cohort. The TRAJ procedure would not group the data using the parameter "neighborhood SES" unless it was found to be a significant discriminatory parameter for the data. As a result of these analyses, group membership was influenced by low neighborhood SES, hypertensive status, age and education. The data were grouped into

three categories of membership as specified, yet there was no method available using the TRAJ procedure to define groupings by neighborhood SES (e.g., low, medium and high) *a priori*. Therefore, we opted to model these longitudinal data using individual growth models, with neighborhood SES as a main exposure, and determine if there were statistical interactions between neighborhood SES and other covariates which influenced a change in slope for the SRH trajectories.

F. Strengths and Limitations

1. Strengths

A strength of the ARIC data is that they include 19 years of annual follow-up contacts (median 17.6) for assessing SRH and a median of 4.2 years of follow-up for rehospitalizations and mortality among participants with an incident hospitalized HF event. Many clinical trials and registry studies do not capture the clinical course of HF subsequent to discharge (Adams et al., 2005; G. C. Fonarow, J. T. Heywood et al., 2007; Fonarow, Srikanthan, Cintron, & Lopatin, 2007; M. Galvao & ADHERE Scientific Advisory Committee (SAC) Investigators, 2005; Marie Galvao et al., 2006; Heywood et al., 2007) or otherwise short-term follow-up (Felker et al., 2004; Gregg C. Fonarow et al., 2007; Gheorghiade et al., 2006; B. H. Greenberg et al., 2007). An additional limitation of clinical trials is that they do not typically enroll a representative sample of HF patients. For example, data from clinical trials indicate that women represent approximately one-third of patients (Marie Galvao et al., 2006). Conversely, among studies utilizing registry data, approximately half of all HF patients are women. Similarly, women make up nearly half of incident HF cases in the ARIC cohort (Loehr et al., 2008).

An additional strength of these data for investigating time until rehospitalization or death is the continuous monitoring of cohort participants for rehospitalizations occurring for any reason at any time during follow-up. We utilized data provided by annual follow-up in order to conduct time-to-event analyses, which tracked participants after an incident HF hospitalization until they experienced a rehospitalization or death or were censored. The ARIC study design allowed for thorough ascertainment of rehospitalizations, deaths and dates of last contact. We also utilized an alternative method for analyzing these rehospitalization and death data in order to make the results comparable to studies which have limited follow-up time, or that only assess whether participants have been rehospitalized at discrete time points (e.g., 30 days post-discharge).

These data were also ideal for use with regard to SRH. We were able to transform the SRH scale per Diehr et al (Paula Diehr & Patrick, 2003). This transformation is superior to the use of ordinal values, since it takes into consideration the non-linear relationship between *excellent*, *good*, *fair* and *poor*. Researchers have also grouped measures of SRH, such as *excellent*/*good* and *fair*/*poor* together for analyses (Daponte-Codina et al., 2008; McFadden et al., 2008; Wight et al., 2008). This technique is intended to dichotomize *good* and *poor* health, yet also over-simplifies the relationship, and may obscure true gradients in SRH between levels. Another advantage with regard to the transformation of SRH values is that the transformation adequately accounts for death, and allows for meaningful interpolation of SRH values if a participant is missing a SRH value from an interim AFU.

Further, Kreiger et al. provided preliminary data in support of the use of US census tract variables based on economic indicators (e.g., income, poverty) for the study of neighborhood SES and adverse health outcomes (N. Krieger et al., 2003). Results from the Public Health

Geocoding Disparities Project (N. Krieger et al., 2003) suggested that individual neighborhood SES measures captured the neighborhood economic environment as well as more complex composite indexes. Previous research in ARIC community surveillance also supports our selection of a single US census tract variable, *median household income*, to represent neighborhood SES for these analyses. In a comparison of three single-variable measures (median household income, percent below poverty and percent of households headed by women) and one composite index (A. V. Diez-Roux et al., 2001), relationships between neighborhood SES and incident hospitalized MI were consistent across neighborhood SES measures (Abstracts of the 41st Annual Meeting of the Society for Epidemiologic Research June 24-27, 2008, 2008). In a study of incident hospitalized MI rates across all four ARIC study communities, the association with neighborhood SES were consistent using either overall (community-wide), community-specific or race-specific cutpoints for *median household income* (Kathryn M. Rose et al., 2009). For the purpose of this study, we used community-wide cutpoints to capture the influence of *median household income*, since overall cutpoints better represent the income distribution of the study population from which the cohort was sampled.

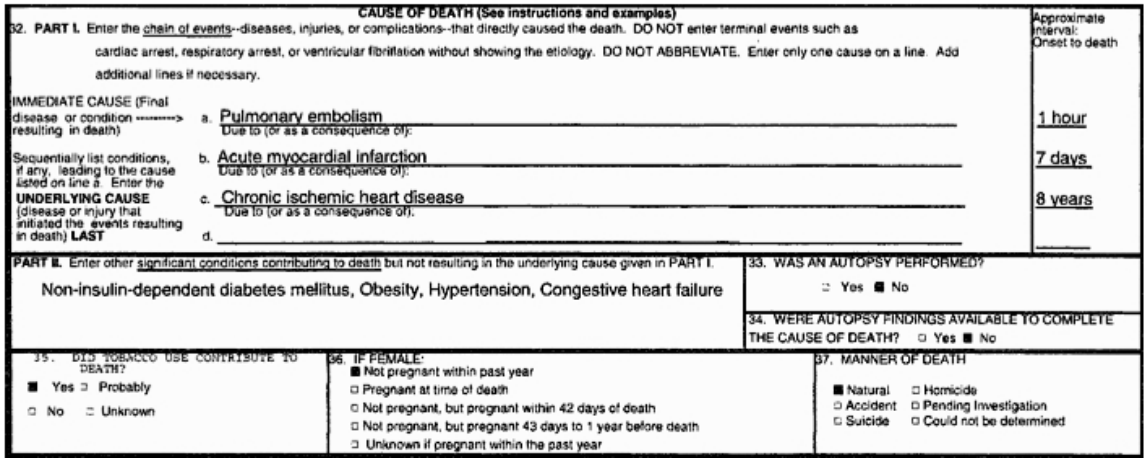
When we included a tract-level neighborhood SES measure in the statistical models, we accounted for the dependence of observations among participants from the same census tract of residence. Otherwise, the standard error of the estimates would have been underestimated. Multilevel modeling adjusts the standard error of the estimates to allow for the dependence of observations within the same cluster. We were able to include participant characteristics as the first level of analysis clustered within census tracts as second-level units. We reported the presence or absence of an association between neighborhood SES and HF progression,

and did not attempt to make a direct causal inference due to the hierarchical structure of the analysis (Greenland, 2002; Greenland & Brumback, 2002; Oakes, 2004). Failing to account for the clustering of participants in census tracts may obscure some important neighborhood effects. For example, in the National Heart Care Project, one-year mortality was found to be greater in whites than blacks among Medicare enrollees with incident HF developing chronic kidney disease during follow-up. However, upon adjusting for state and hospital cluster, racial differences disappeared, indicating a greater influence of geography in the analyses (Smith et al., 2005). The use of generalized estimation equations also accounted for the clustering of hospitalizations within patients, as some of the analyses involved repeated measures data.

Cause of death data are difficult to quantify with respect to HF, since HF is rarely listed as an underlying cause of death (Murdoch et al., 1998). According to guidelines for completing death certificates (CDC, 2003, 2004), congestive HF is a broad differential diagnosis and cannot be listed as an underlying cause of death, since its etiology should always follow its mention on the death certificate (**Figure 4.5**). **Figure 4.5** shows two examples of how HF may be validly recorded on a death certificate – either as a significant condition contributing to death or as an immediate cause of death, with named underlying etiology. Often death certificates neglect to mention HF, and are insensitive to capturing a prior history of HF (Anthony et al., 2009). As a result, the number of persons dying with HF is likely to be underestimated if using death certificate data.

Figure 4.5. Two examples of heart failure recorded correctly on death certificates

HF as a significant condition contributing to death



CAUSE OF DEATH (See instructions and examples)

32. PART I. Enter the chain of events--diseases, injuries, or complications--that directly caused the death. DO NOT enter terminal events such as cardiac arrest, respiratory arrest, or ventricular fibrillation without showing the etiology. DO NOT ABBREVIATE. Enter only one cause on a line. Add additional lines if necessary.

Approximate interval: Onset to death

IMMEDIATE CAUSE (Final disease or condition ---------> resulting in death)
a. Pulmonary embolism — Due to (or as a consequence of): — 1 hour

Sequentially list conditions, if any, leading to the cause listed on line a. Enter the UNDERLYING CAUSE (disease or injury that initiated the events resulting in death) LAST
b. Acute myocardial infarction — Due to (or as a consequence of): — 7 days
c. Chronic ischemic heart disease — Due to (or as a consequence of): — 8 years
d. ____

PART II. Enter other significant conditions contributing to death but not resulting in the underlying cause given in PART I.

Non-insulin-dependent diabetes mellitus, Obesity, Hypertension, Congestive heart failure

33. WAS AN AUTOPSY PERFORMED? ☐ Yes ■ No

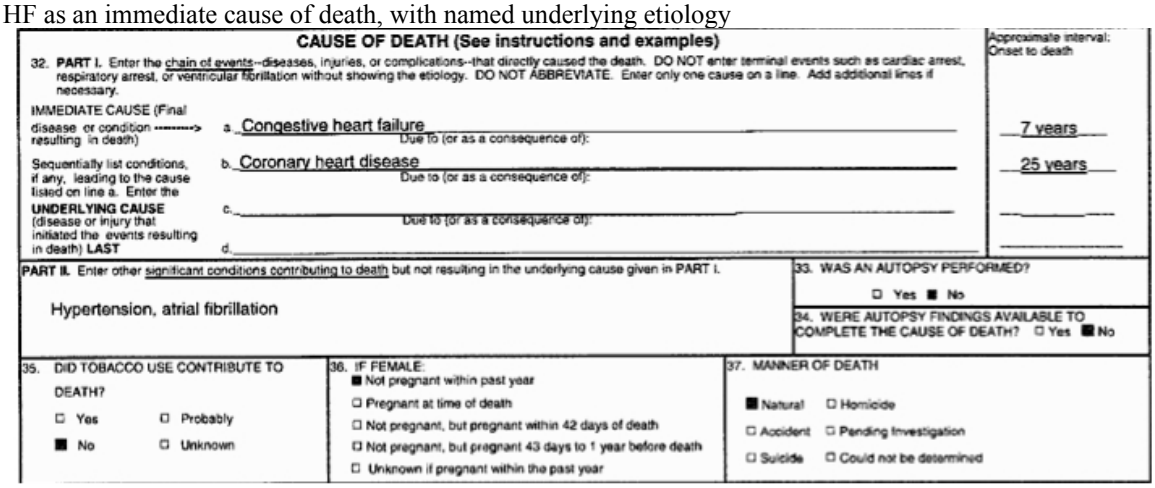
34. WERE AUTOPSY FINDINGS AVAILABLE TO COMPLETE THE CAUSE OF DEATH? ☐ Yes ■ No

35. DID TOBACCO USE CONTRIBUTE TO DEATH?
■ Yes ☐ Probably
☐ No ☐ Unknown

36. IF FEMALE:
■ Not pregnant within past year
☐ Pregnant at time of death
☐ Not pregnant, but pregnant within 42 days of death
☐ Not pregnant, but pregnant 43 days to 1 year before death
☐ Unknown if pregnant within the past year

37. MANNER OF DEATH
■ Natural ☐ Homicide
☐ Accident ☐ Pending Investigation
☐ Suicide ☐ Could not be determined

HF as an immediate cause of death, with named underlying etiology



CAUSE OF DEATH (See instructions and examples)

32. PART I. Enter the chain of events--diseases, injuries, or complications--that directly caused the death. DO NOT enter terminal events such as cardiac arrest, respiratory arrest, or ventricular fibrillation without showing the etiology. DO NOT ABBREVIATE. Enter only one cause on a line. Add additional lines if necessary.

Approximate interval: Onset to death

IMMEDIATE CAUSE (Final disease or condition ---------> resulting in death)
a. Congestive heart failure — Due to (or as a consequence of): — 7 years

Sequentially list conditions, if any, leading to the cause listed on line a. Enter the UNDERLYING CAUSE (disease or injury that initiated the events resulting in death) LAST
b. Coronary heart disease — Due to (or as a consequence of): — 25 years
c. ____ — Due to (or as a consequence of): ____
d. ____

PART II. Enter other significant conditions contributing to death but not resulting in the underlying cause given in PART I.

Hypertension, atrial fibrillation

33. WAS AN AUTOPSY PERFORMED? ☐ Yes ■ No

34. WERE AUTOPSY FINDINGS AVAILABLE TO COMPLETE THE CAUSE OF DEATH? ☐ Yes ■ No

35. DID TOBACCO USE CONTRIBUTE TO DEATH?
☐ Yes ☐ Probably
■ No ☐ Unknown

36. IF FEMALE:
■ Not pregnant within past year
☐ Pregnant at time of death
☐ Not pregnant, but pregnant within 42 days of death
☐ Not pregnant, but pregnant 43 days to 1 year before death
☐ Unknown if pregnant within the past year

37. MANNER OF DEATH
■ Natural ☐ Homicide
☐ Accident ☐ Pending Investigation
☐ Suicide ☐ Could not be determined

(CDC, 2003)

However, a focus of the current research is all-cause mortality among participants with HF. Our inclusion criteria specify that participants develop incident hospitalized HF over the course of follow-up. Therefore, the analyses presented in this work do not rely on death certificate information regarding cause of death, nor were death certificates used to determine if participants had HF. Thus, readers can assume that if the death certificates were completed accurately for these individuals, HF would be listed as a significant condition contributing to death or as an immediate cause of death.

As completeness of SRH data depend upon multiple measures pre- and post-event diagnosis, low loss to follow-up is important. In the ARIC cohort, according to ARIC coordinating center communication, approximately 93% of living participants were contacted in year 19 of the study and did not refuse to participate. Therefore, in reference to AFU data used in the current study, only 7% of ARIC cohort participants have been lost to follow-up.

With regard to our assessment of clinical variables, hypertension and overweight/obesity data were collected at baseline, prior to the incident HF admission. An advantage of utilizing baseline values instead of medical record data is that the presenting level of blood pressure may not be indicative of typical blood pressure levels, and overweight or obesity upon hospital admission may be due to fluid retention/edema. Furthermore, burden of comorbidity, as determined by the modified Charlson index (Senni et al., 2006) which excludes the point value for congestive HF, was assessed for the current study by searching hospital discharge codes from the incident HF hospitalization. It is well-documented that hospital discharge data provide limited information regarding conditions other than those involving the principle diagnosis (J.G.F Cleland et al., 2003; D. S. Lee et al., 2005). As a result, many studies utilizing the Charlson index have included comorbidities from all hospital admissions associated with a particular condition (Cleves et al., 1997), or during the one year (Deyo et al., 1992) or five years (Blackledge et al., 2003; S. Stewart et al., 2002) prior to the hospitalization of interest. A strength of our study is that we were able to construct the modified Charlson index utilizing information from hospitalizations up to five years' prior to the incident HF hospitalization to see how the distribution of comorbidity in our sample changed (**Table 4.3**). Data from the index hospitalized HF event was used because all patients had those data available. If data from prior years were used, the subset

of patients with prior hospitalizations would have had more opportunities to have comorbidities listed in the discharge summary, yet may not have truly had a higher burden of comorbidity than those patients first identified during the index HF hospitalization.

Table 4.3. Prevalence (%) of Charlson comorbidity index components during the index and prior to the index heart failure hospitalization, The ARIC study (1987-2004)

		Incident HF hospitalization N=1,342	1 year prior N=512	2 years prior N=674	3 years prior N=793	4 years prior N=877	5 years prior N=917
Myocardial infarction	Y	12.7	17.0	16.6	15.6	16.5	16.6
	N	87.3	83.0	83.4	84.4	83.5	83.4
Peripheral vascular disease	Y	7.8	5.7	5.0	5.0	4.7	4.7
	N	92.2	94.3	95.0	95.0	95.3	95.3
Cerebrovascular disease	Y	9.0	7.8	7.6	6.3	6.4	7.0
	N	91.0	92.2	92.4	93.7	93.6	93.0
Dementia	Y	0.6	0.2	0.5	0.3	0.2	0.2
	N	99.4	99.8	99.5	99.7	99.8	99.8
Chronic pulmonary disease	Y	27.4	13.7	11.1	11.4	11.3	11.3
	N	72.6	86.3	88.9	88.6	88.7	88.7
Rheumatologic disease	Y	2.5	2.2	1.6	1.3	1.3	1.2
	N	97.5	97.8	98.4	98.7	98.7	98.8
Mild liver disease	Y	0.8	0.4	0.3	0.3	0.2	0.2
	N	99.2	99.6	99.7	99.7	99.8	99.8
Diabetes	Y	21.8	21.1	20.4	19.2	20.0	19.2
	N	78.2	78.9	79.6	80.8	80.0	80.8
Diabetes with end organ damage	Y	4.1	2.9	2.1	1.5	1.3	0.1
	N	95.9	97.1	97.9	98.5	98.7	99.9
Hemiplegia or paraplegia	Y	1.5	1.4	0.7	0.5	0.8	0.9
	N	98.5	98.6	99.3	99.5	99.2	99.1
Moderate or severe kidney disease	Y	2.8	1.2	0.5	0	0.1	0.2
	N	97.2	98.8	99.5	100	99.9	99.8
Moderate or severe liver disease	Y	0.6	0.2	0	0.1	0.1	0
	N	99.4	99.8	100	99.9	99.9	100
Index score of ≥2+	Y	23.4	18.6	15.6	13.9	14.4	14.0
	N	76.6	81.4	84.4	86.1	85.6	86.0
Index score	0	35.3	60.9	62.9	64.8	64.1	63.9
	1	41.3	20.5	21.5	21.3	21.6	22.1
	2	16.0	11.1	11.1	10.3	10.8	10.6
	3	3.5	5.3	3.1	2.8	2.6	2.6
	4	2.9	1.2	1.0	0.4	0.6	0.7
	5	0.9	1.0	0.3	0.4	0.4	0.7
	6	0.1	-	-	-	0.1	0.1

2. Limitations

Annual follow-up and ongoing surveillance of the ARIC cohort participants allowed for the identification of hospitalized incident HF cases occurring since baseline. It is hypothesized that the prognosis for hospitalized HF patients is worse than for patients diagnosed in the community (Blackledge et al., 2003). Although data is currently collected on out-of-hospital management of HF in the ARIC cohort, acquisition of these data has only recently begun, and were not available for this analysis. Therefore, the results of these analyses are most generalizable to those HF events occurring in-hospital, and may not be representative of cases occurring in the community outpatient setting.

In the ARIC cohort, incident hospitalized HF is identified by a HF diagnostic code *428.0-428.9* in any position in the hospital discharge record, and is not validated by physician adjudication. Abstractors are instructed to record discharge codes as they appear in the hospital record, yet no particular order of codes is specified in the instructions for the abstractors (ARIC, 2007b). Therefore, the position of the discharge code (e.g., first or second position) may not be reliable in ARIC. A limitation of these data, then, is an inability to determine how salient the HF diagnosis was to the hospitalization in question.

Alternatives to the use of discharge codes in the diagnosis of HF are physical exams or physician review of hospital records to validate the diagnosis. Physical exams were conducted in the ARIC cohort at baseline (1987-1989) and at three in-person visits thereafter. However, the last visit was held in 1998, and there are no physical exam data for the ARIC cohort after that time. In general, methods for diagnosing HF via physical exam are varied (Fonseca, 2006; van Kraaij et al., 2002) and depend on clinical findings not easily identified

nor commonly looked for during a physical exam (Kirkpatrick & Lang, 2008; Young & Worthley, 2004). Physician adjudication of HF events in the ARIC cohort is currently underway for discharge records abstracted since 2007 (ARIC, 2007c). Physician review of medical records requires availability of trained study personnel and is an added expense to monitor.

According to Goff et al. (2000), the ICD-9-CM code *428* in the first or second discharge diagnosis position among hospitalized MI patients in the Corpus Christi Heart Project was associated with 63% sensitivity, 95% specificity, 84% positive predictive value and 87% negative predictive value. In comparison with an algorithm including both *428* and *402* codes (67% sensitivity, 93% specificity, 77% positive predictive value and 88% negative predictive value), the use of code *428* to identify HF resulted in a 25% underestimate of HF-related hospitalizations (vs. 13%). However, Shahar et al. (2004) found 85% of hospitalizations coded as HF (ICD-9-CM *428*) met the majority of HF definitions per published criteria (Shahar et al., 2004). Further, in a community-based cohort study, Roger et al. found that the ICD-9-CM code *428* identified 80% of the HF cases, and 82% of these cases also met Framingham criteria for HF. In comparison, other ICD-9-CM HF codes that were not used in conjunction with a *428* code met Framingham criteria for HF in only 14-30% of the cases (Roger et al., 2004).

Inaccuracies in identifying HF hospitalizations with the use of ICD-9-CM codes have implications with regard to this project. Specifically, it is concerning that the use of the discharge diagnosis code *428* may not adequately capture the hospitalized burden of HF among ARIC cohort members. However, heart failure signs and symptoms were not assessed during physical examinations of participants over the course of the ARIC study, so a

gold standard definition of HF as used in other studies (Goff et al., 2000) is not applicable to the proposed project. Data are currently being collected on outpatient diagnosis of heart failure among ARIC cohort members. In the future it will be possible to assess, as these outpatient data become available, whether participants identified with HF on an outpatient basis have also been identified with HF as an inpatient according to hospital records.

Although there is concern regarding correctly identifying incident hospitalized HF in the study population using ICD-9-CM discharge codes, data which also accurately capture subsequent hospitalizations are necessary. While it is probable that incident hospitalized HF events were underestimated in the ARIC cohort, the assessment of repeat hospitalizations is likely biased in the other direction. Repeat hospitalizations for HF are undoubtedly a burden on the health care system, however, it is likely that more hospitalizations are attributed to HF than are actually due to the condition. An important limitation of utilizing hospital record data is that once an individual receives a diagnosis code for HF on their hospital discharge report, the HF diagnosis code is often reassigned, or carried over, to subsequent hospitalizations at that hospital, even if the primary reason for the rehospitalization is not HF. Therefore, the current study assesses all-cause, CVD- and HF-related rehospitalizations, respectively, in order to represent a range of plausible values for rehospitalization rates among participants with an incident hospitalized diagnosis of HF.

G. IRB/ Human Subjects

Approval for this project was obtained through the Institutional Review Board of the University of North Carolina Gillings School of Global Public Health. No additional contact

was made with study participants, as all analyses were of secondary data. The ARIC study coordinators at each clinic site obtained approval for data collection.

V. Socioeconomic Status, Medicaid Coverage, Clinical Comorbidity and Rehospitalization or Death following an Incident Heart Failure Hospitalization: ARIC Cohort (1987-2004)

The first manuscript prepared and submitted to a peer-reviewed journal incorporated two aspects of HF progression: rehospitalization and mortality. With respect to the dissertation outline, this manuscript presents the results and discusses the implications of Aims 1 and 2.

The concepts of rehospitalization and mortality work well together as a body of work, since both outcomes are a result of severe or decompensated HF. This manuscript adds to the literature, since existing studies of morbidity and mortality are limited by short-term follow-up. In addition, reports based on clinical trials often explore *rehospitalization or mortality* as a composite endpoint, yet rehospitalization and mortality represent distinct entities, and warrant individual evaluation.

A. ABSTRACT

Repeat hospitalizations among persons with heart failure (HF) are often due to a worsening of HF symptoms and are a burden on the health care system. A short time to rehospitalization or death among HF patients may be a marker of severe disease, inadequate outpatient management of HF symptoms, or both. We compared the association of neighborhood median household income (nINC) and receipt of Medicaid with rehospitalization or death among Atherosclerosis Risk in Communities cohort study

participants following an incident HF hospitalization (1987-2004). We categorized 1990 US Census tract-level nINC into tertiles based upon participants' place of residence at baseline, and used generalized linear Poisson mixed models to estimate rehospitalization rate ratios and 95% confidence intervals (RR, 95% CI), accounting for clustering within census tracts. We used Cox regression to estimate hazard ratios (HR, 95% CI) of rehospitalization or death. We assessed for effect measure modification by sociodemographic and clinical variables, and comorbidity burden significantly modified the nINC-rehospitalization/mortality relationship. Of 1,342 incident HF patients, 89% were rehospitalized, 47% died, and 91% were rehospitalized or died by the end of 2004. In models controlling for race/study community, gender, age at HF diagnosis, body mass index, hypertension, educational attainment, alcohol use and smoking, persons with a high burden of comorbidity who were living in low nINC areas at baseline had an elevated hazard for all-cause rehospitalization (1.40, 1.10-1.77), death (1.36, 1.02 -1.80), rehospitalization or death (1.36, 1.08-1.70) – as well as increased rates of all-cause and cardiovascular disease-related hospitalizations – compared to those with a high burden of comorbidity living in high nINC areas. Meanwhile, Medicaid recipients with a low level of comorbidity had an increased hazard of all-cause rehospitalization (1.19, 1.05 -1.36) and rehospitalization or death (1.21, 1.07-1.37), and a higher rate of repeat hospitalizations compared to non-Medicaid recipients. In summary, participants from low nINC areas with a high burden of comorbidity were at greater risk for rehospitalization or death following a HF diagnosis, while Medicaid recipients with a low comorbidity burden were rehospitalized more often. Comorbidity burden appears to influence the association between nINC, Medicaid status and rehospitalization and death among HF patients.

B. INTRODUCTION

Hospital discharges for heart failure (HF) increased 157% from 1979 to 2002 (*Heart Disease and Stroke Statistics - 2005 Update*, 2005), and continue to rise (D. Lloyd-Jones et al., 2010). HF rehospitalizations, which are often preventable (MedPAC, 2007), tend to be higher among older patients, non-whites, and patients with prior hospitalizations and multiple primary care visits (Fang et al., 2008; Ghali et al., 1990; Inouye et al., 2008; Schocken et al., 2008). In addition to being recognized as a major cause of serious morbidity (Adams et al., 2005; Cowie et al., 2002; H. Eriksson, 1995; Hoyt & Bowling, 2001), HF mortality is high (Jong et al., 2002; M. S. Nieminen & Harjola, 2005). From 1980 to 1995, the number of deaths in the US with an underlying cause of HF increased nearly 70% (Haldeman et al., 1999). HF is a primary or contributory cause of more than 300,000 deaths each year in the US (Hunt et al., 2001), and HF mortality rates increase sharply with age.

Among Atherosclerosis Risk in Communities (ARIC) study (1987-2002) cohort members with incident HF, 30-day mortality was 10%, while one- and five-year mortality was 22% and 42%, respectively (Loehr et al., 2008). Several studies with a combined endpoint of rehospitalization or mortality report a prevalence of rehospitalization or death of 31-35% at 60 days (Felker et al., 2004; O'Connor et al., 2005), and 81% (Zannad et al., 1999) at one year.

A shorter interval of time between initial hospitalization for HF and readmission or death may be an indicator of poor patient health and more severe disease. Patients diagnosed with HF often have coexisting clinical comorbidities. Chronic conditions such as hypertension, coronary heart disease (CHD), diabetes and obesity are risk factors for the development of

HF (Schocken et al., 2008; Weir et al., 2006), and clinical HF is commonly accompanied by one or more of these factors (Heywood et al., 2007). In general, the burden of mortality (Charlson et al., 1987; Deyo et al., 1992; Jong et al., 2002) and rehospitalization (Philbin & DiSalvo, 1999) increases with increasing comorbidity. However, in populations, variations in HF morbidity and mortality are not completely explained by clinical features of the disease (Fonarow, 2008), suggesting the need to explore understudied domains, such as the influence of the socioeconomic context.

Low socioeconomic status is associated with higher HF incidence (He et al., 2001; Ingelsson et al., 2006; F. A. McAlister et al., 2004; Schaufelberger & Rosengren, 2007; S. Stewart et al., 2006), rehospitalization and survival (Philbin et al., 2001; Rathore et al., 2006; S. Stewart et al., 2002; Simon Stewart et al., 2001; Wen & Christakis, 2005). Meanwhile, health insurance status is associated with care-seeking behavior (Go et al., 2006; Philbin & DiSalvo, 1999) and subsequent disease outcomes (Ayanian et al., 1993). Medicaid, in particular, may exert effects on health outcomes which are independent of socioeconomic status (Foraker et al., 2008; Ross & Mirowsky, 2000), as its receipt is determined by having certain diseases and disabilities or an income below the poverty line (Ku, 2005; Rosenbaum, 2002). Evidence suggests that social and environmental contexts play an important role in health outcomes (Ana V Diez Roux et al., 2004; Nancy Krieger et al., 2002; Marmot, 2003), however, research to date has not assessed the influence of neighborhood socioeconomic status or receipt of Medicaid on the risk of rehospitalization or mortality among HF patients in the context of individual socioeconomic, demographic and comorbid factors. We examined the role of neighborhood SES in rehospitalization or death after initial HF events in the ARIC study.

C. MATERIALS AND METHODS

ARIC cohort participants (N=15,792) were enrolled from 1987-1989 from the following four US communities: Forsyth County, North Carolina; Washington County, Maryland; suburbs of Minneapolis, Minnesota and Jackson, Mississippi (The Atherosclerosis Risk in Communities (ARIC) study: design and objectives, 1989). Cohort members are contacted yearly, regardless of whether or not they continue to reside within the study boundaries. As part of annual follow-up, information regarding inpatient hospital stays is collected, and hospitalization data are abstracted from the medical record.

All-cause hospitalizations are identified during annual follow-up or during routine ARIC community surveillance (White et al., 1996). For the current study, cardiovascular disease (CVD)-related hospitalizations were further identified from all-cause hospitalizations using International Classification of Diseases, Version 9 (ICD-9) discharge codes *402*, *410-414*, *427*, *428*, *430-436* or *518.4*; while a HF-related hospitalization was defined as that with an ICD-9 discharge code *428* (ARIC, 2007a).

Participants' addresses obtained at baseline were assigned to the level of the census tract by a vendor with high geocoding accuracy (Whitsel et al., 2004). The 1990 US census tract-level neighborhood-level socioeconomic measure selected for study was median household income (nINC). In previous work, the use of the single-variable nINC measure produced results of similar magnitude and precision when compared to a more complex composite index measure of neighborhood SES (Kathryn M. Rose et al., 2009). We categorized nINC into community-wide tertiles based upon participants' place of residence at baseline, during the period 1987-1989: low (<$24,777), medium ($24,777≤-<36,071) and high (≥$36,071).

We did not take into account whether or not cohort members changed their address from baseline, as the study population was relatively stable. Unpublished data indicate that of participants with complete address information through visit three, 84% had lived in the same census tract since baseline, and even if they changed place of residence, 92% of participants remained in the same nINC tertile throughout follow-up.

After excluding 245 participants with prevalent HF at baseline, 1,415 participants had an incident hospitalized HF event through 2004. An additional 70 participants were excluded due to missing data on neighborhood socioeconomic status, and 3 were excluded because they were not white or black, or were blacks living in Minnesota or Maryland, resulting in a final sample size of 1,342 participants.

Covariates included race/study community, gender, age at incident HF hospitalization and selected socioeconomic, clinical and behavioral characteristics. Educational attainment was assessed at baseline (less than 11 years, high school graduate, and greater than high school), as was health insurance status at the time of the index HF hospitalization (receipt of Medicaid, yes/no). Participants' body mass index (BMI) was assessed at baseline and classified as normal (<25 kg/m^2), overweight (25-<29.9 kg/m^2) or obese (≥ 29.9 kg/m^2). Hypertensive status at baseline was identified as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or taking hypertensive medication within the previous two weeks. Teaching status of the hospital during the index admission (teaching vs. non-teaching), was based upon whether or not the hospital has an internal medicine residency training program.

We ascertained the prevalence of common underlying conditions at the time of the index HF hospitalization using ICD-9 discharge codes. The Charlson Index, a clinical comorbidity algorithm (Deyo et al., 1992), was derived from these data (Table 2). The Charlson Index is a validated measure used to quantify the burden of comorbidity in several studies of mortality and adverse health outcomes (Charlson et al., 1987; Deyo et al., 1992). In its use with HF outcomes, a "modified" Charlson Index excludes chronic HF from the conditions included in the computation of the comorbidity score (Senni et al., 2006). Consistent with previous studies, we defined a high burden of comorbidity as a sum of two or more points on the Charlson Index scale, whereas a low burden of comorbidity was defined with a total of zero to one points.

We used generalized linear Poisson mixed models to estimate all-cause, CVD-related and HF-related rehospitalization rate ratios, comparing the rates of participants from low nINC to high nINC, medium nINC to high nINC and Medicaid recipients to non-Medicaid recipients, along with 95% confidence intervals (RR, 95% CI). This modelling strategy accounted for repeat hospitalizations among patients as well as the clustering of patients within census tracts. Time at risk for rehospitalization was the time elapsed between the incident HF hospitalization admission date and death, loss to follow-up or the end of 2004, whichever came first. We assessed for over-dispersion by consulting the deviance statistic of the Poisson model, and conducted supplementary analyses using negative binomial regression when the deviance statistic exceeded one (Dallal, 2008; Rao & Scott, 1999).

The product-limit (Kaplan-Meier) method was used to measure time to readmission, death, or readmission or death over the course of follow-up. Multivariate Cox proportional hazard models estimated the risk of death or rehospitalization or death, and rehospitalization

alone using death during follow-up as the censoring variable. The model produced survival curves depicting survival free of readmission or death, and the proportional hazards assumption was assessed. All participants were censored at the end of 2004.

Crude nINC-rehospitalization/mortality analyses were conducted, the influence of covariates in a full model were tested, and effect modification ($p_{interaction}<0.05$) of the nINC-rehospitalization/mortality relationship was assessed by age, race/study community, gender, hypertension, BMI and comorbidity index score.

D. RESULTS

Among participants with an incident HF hospitalization, approximately half (46%) were female, one-third (33%) were black and the average age at the time of the index event was 67 years. As shown in **Table 5.1**, a greater proportion (55%) of participants from low nINC areas had attained 11 or fewer years of education, as compared to participants in medium (35%) and high (19%) nINC areas. Twenty percent of participants living in low nINC areas were Medicaid recipients, in contrast to 3% of those living in medium and high nINC areas (**Table 5.1**).

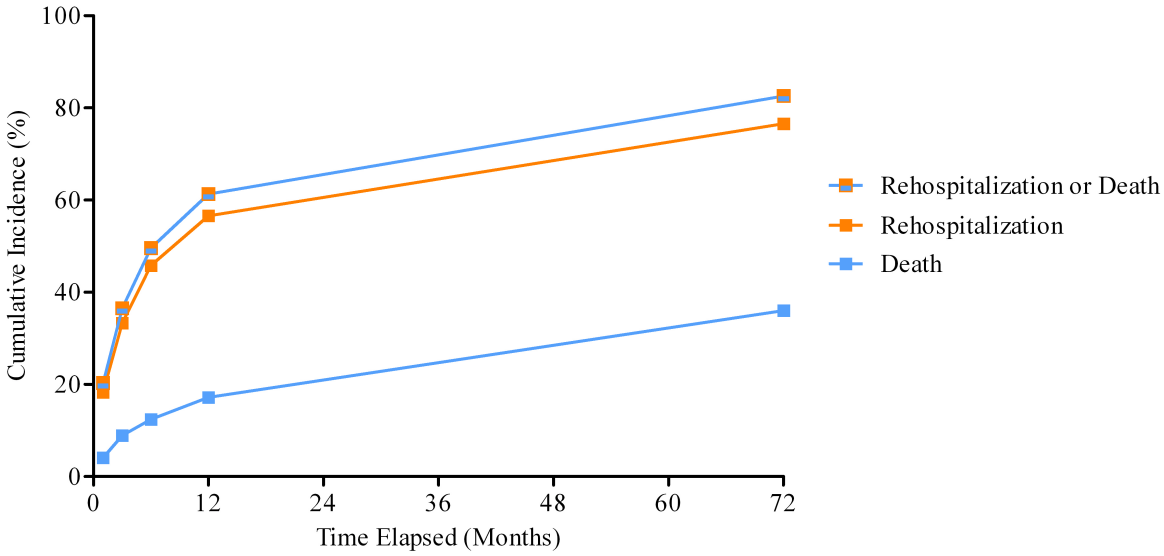
Table 5.1. Characteristics of participants with an incident hospitalized heart failure event (n=1,342), The ARIC study (1987-2004)

	Medicaid Recipient				Median Household Income (nINC)					
	Yes N=135		No N=1,207		Low N=553		Medium N=454		High N=335	
	N	%	N	%	N	%	N	%	N	%
Characteristics at Baseline										
Median Household Income, mean	17,897		29,456		16,519		31,799		42,979	
Gender										
Female	97	71.9	513	42.5	309	55.9	173	38.1	128	38.2
Male	38	28.1	694	57.5	244	44.1	281	61.9	207	61.8
Race/Study Community										
Black/Forsyth	5	3.7	40	3.3	26	4.7	17	3.7	2	0.6
Black/Jackson	97	71.9	300	24.8	369	66.7	6	1.3	22	6.6
White/Forsyth County	9	6.6	264	21.9	42	7.6	141	31.1	90	26.9
White/Washington County	20	14.8	363	30.1	103	18.6	232	51.1	48	14.3
White/Minneapolis	4	3.0	240	19.9	13	2.4	58	12.8	173	51.6
Hypertensive[a]										
Yes	112	66.3	598	51.0	349	63.1	200	44.1	161	48.1
No	57	33.7	564	48.1	200	36.2	251	55.3	170	50.8
Missing	-	-	11	0.9	4	0.7	3	0.7	4	1.1
Body Mass Index (BMI)[b]										
Obese	75	55.6	503	41.7	273	49.4	172	37.9	133	39.7
Overweight	37	27.4	447	37.0	186	33.6	173	38.1	125	37.3
Normal	23	17.0	255	21.1	93	16.8	109	24.0	76	22.7
Missing	-	-	2	0.2	1	0.2	-	-	1	0.3
Current Drinker										
Yes	32	23.7	589	48.8	168	30.4	237	52.2	216	64.5
No	103	76.3	618	51.2	385	69.6	217	47.8	119	35.5
Current Smoker										
Yes	56	41.5	417	34.5	204	36.9	161	35.5	108	32.2
No	79	58.5	790	65.5	349	63.1	293	64.5	227	67.8
Educational Attainment (years)										
Advanced (17-21)	12	8.9	307	25.4	79	14.3	106	23.4	134	40.0
Intermediate (12-16)	26	19.3	472	39.1	169	30.6	190	41.9	139	41.5
Basic (≤11)	96	71.1	425	35.2	302	54.6	157	34.5	62	18.5
Missing	1	0.7	3	0.3	3	0.5	1	0.2	-	-
Characteristics at Index Hospitalization										
Age, mean (SD)	67.5 (6.1)		66.9 (6.9)		66.0 (6.8)		67.9 (6.6)		67.5 (6.9)	
Charlson Comorbidity Index Score[c]										
≥2	37	27.4	277	23.0	126	22.8	118	26.0	70	20.9
<2	98	72.6	930	77.0	427	77.2	336	74.0	265	79.1
Medicaid Recipient[d]										
Yes	-	-	-	-	111	20.1	15	3.3	9	2.7
No	-	-	-	-	442	79.9	439	96.7	326	97.3

[a]Systolic blood pressure ≥140mmHg or diastolic blood pressure ≥90mmHg, or blood pressure medication in the last two weeks.
[b]Normal BMI: <25kg/m^2; overweight: 25-<29.5kg/m^2; and obese: ≥29.5kg/m^2
[c]Adapted for use with ICD-9 discharge codes
[d]As indicated in medical record

By the end of 2004, 89% of participants with an incident HF hospitalization had been rehospitalized at least once (mean: 3.6; range: 0-47), 47% died, and 91% had been rehospitalized or had died. **Figure 5.1** shows life table trends of rehospitalization, death and rehospitalization or death by person-time elapsed since the incident hospitalized HF event. At 30 days, 19% had been rehospitalized, while at 6 months 13% had died, and at one year, 62% had been rehospitalized or had died (**Figure 5.1**).

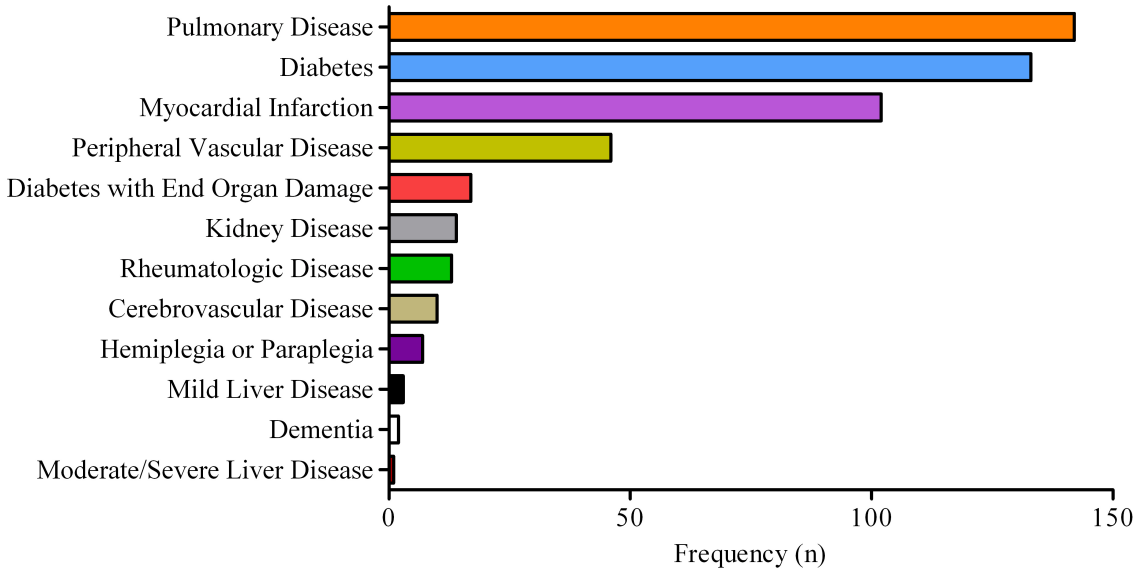
Figure 5.1. Cumulative proportion of participants with an incident heart failure hospitalization experiencing rehospitalization, death and rehospitalization or death, The ARIC study (1987-2004)



Almost one-quarter of participants had a comorbidity index score of two or greater (Table 1). Charlson comorbidity index components and their associated point values are shown in **Table 3.2**. The most common comorbidities identified at the index hospitalization were chronic pulmonary disease (27%), diabetes (22%) and myocardial infarction (13%). **Figure 5.2** shows the prevalence of each of the comorbidity index components at the index hospitalization. The comorbidity index score modified the nINC-rehospitalization/mortality

relationship in Cox proportional hazards (time-to-event) and Poisson (rate) analyses. Therefore, subsequent results are presented stratified by level of the comorbidity score (≥2 vs. <2).

Figure 5.2. Number of participants with prevalent comorbid disease during the incident HF hospitalization, Charlson index of comorbidity: The ARIC study (1987-2004)

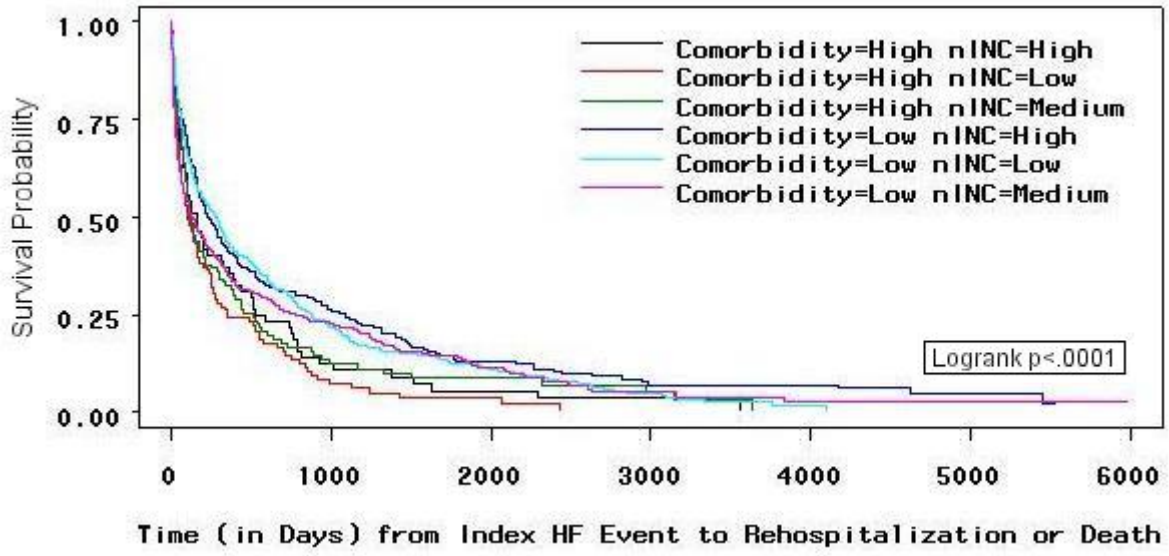


Time-to-event analyses

Crude median rehospitalization- and mortality-free survival times, in days, varied by comorbidity index score (high vs. low) among participants in each nINC tertile [low nINC (107 vs. 283), medium nINC (118 vs. 128) and high nINC (161 vs. 229)] as well as by receipt of Medicaid [recipients (60 vs. 168), those not receiving Medicaid (133 vs. 217)]. Participants with a high burden of comorbidity experienced shorter times to rehospitalization and death compared to participants with a low burden of comorbidity across nINC and Medicaid groups. **Figure 5.3** shows survival curves adjusted for age, race/study community, and gender, and stratified by comorbidity index score and level of nINC. Among participants

with a high burden of comorbidity, those living in high nINC areas experienced the longest rehospitalization- and mortality-free survival, while those living in low nINC areas experienced the shortest. The observed nINC gradient did not persist among participants with a low burden of comorbidity (**Figure 5.3**). However, survival was most favorable for participants with a low burden of comorbidity who were not Medicaid recipients, and least favorable for participants with a high burden of comorbidity who were Medicaid recipients (data not shown).

Figure 5.3. Survival curve depicting time elapsed from the incident hospitalized heart failure event until rehospitalization or death, by nINC and comorbidity, The ARIC study (1987-2004)



The nINC/Medicaid-rehospitalization/mortality survival relationships (HR, 95% CI) are shown in **Table 5.2**. In models controlling for race/study community, gender, age at HF diagnosis, body mass index, hypertension, educational attainment, alcohol use and smoking, persons with a high burden of comorbidity who were living in low nINC areas at baseline had an elevated risk for all-cause rehospitalization (1.40, 1.10-1.77), death (1.36, 1.02 -1.80) and rehospitalization or death (1.36, 1.08-1.70) compared to those with a high burden of

comorbidity living in high nINC areas. In contrast, participants with a low burden of comorbidity who were living in low nINC areas at baseline did not experience an increased risk for death. Medicaid recipients with a low level of comorbidity had an increased risk of all-cause rehospitalization (1.19, 1.05 -1.36) and rehospitalization or death (1.21, 1.07 -1.37) compared to non-Medicaid recipients with a low level of comorbidity. A significantly lower hazard of death was seen among those with a higher burden of comorbidity living in medium nINC areas compared to those living in high nINC areas (0.74, 0.59-0.93).

Table 5.2. Hazard ratios and 95% confidence intervals for rehospitalization, death or rehospitalization or death among participants with an incident hospitalized heart failure event, The ARIC study (1987-2004)

	Charlson Index Score ≥2		Charlson Index Score <2	
	Model 1[a]	Model 2[b]	Model 1[a]	Model 2[b]
All-cause Rehospitalization				
nINC				
Low	1.23 (1.00, 1.51)	1.40 (1.10, 1.77)	1.13 (1.01, 1.26)	1.16 (1.04, 1.30)
Medium	1.07 (0.91, 1.27)	1.14 (0.95, 1.36)	1.26 (1.15, 1.39)	1.28 (1.16, 1.41)
High	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
Medicaid Recipient				
Yes	1.18 (0.95, 1.46)	1.12 (0.89, 1.40)	1.17 (1.03, 1.32)	1.19 (1.05, 1.36)
No	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
Death				
nINC				
Low	1.34 (1.04, 1.72)	1.36 (1.02, 1.80)	1.12 (0.97, 1.30)	1.09 (0.94, 1.26)
Medium	0.75 (0.61, 0.93)	0.74 (0.59, 0.93)	0.91 (0.79, 1.03)	0.90 (0.78, 1.02)
High	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
Medicaid Recipient				
Yes	0.99 (0.76, 1.30)	0.95 (0.72, 1.25)	1.03 (0.87, 1.23)	0.96 (0.80, 1.14)
No	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
All-cause Rehospitalization or Death				
nINC				
Low	1.23 (1.01, 1.50)	1.36 (1.08, 1.70)	1.09 (0.98, 1.21)	1.13 (1.02, 1.26)
Medium	1.00 (0.85, 1.17)	1.04 (0.87, 1.23)	1.24 (1.13, 1.36)	1.27 (1.15, 1.39)
High	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
Medicaid Recipient				
Yes	1.23 (1.00, 1.51)	1.17 (0.95, 1.45)	1.17 (1.04, 1.32)	1.21 (1.07, 1.37)
No	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)

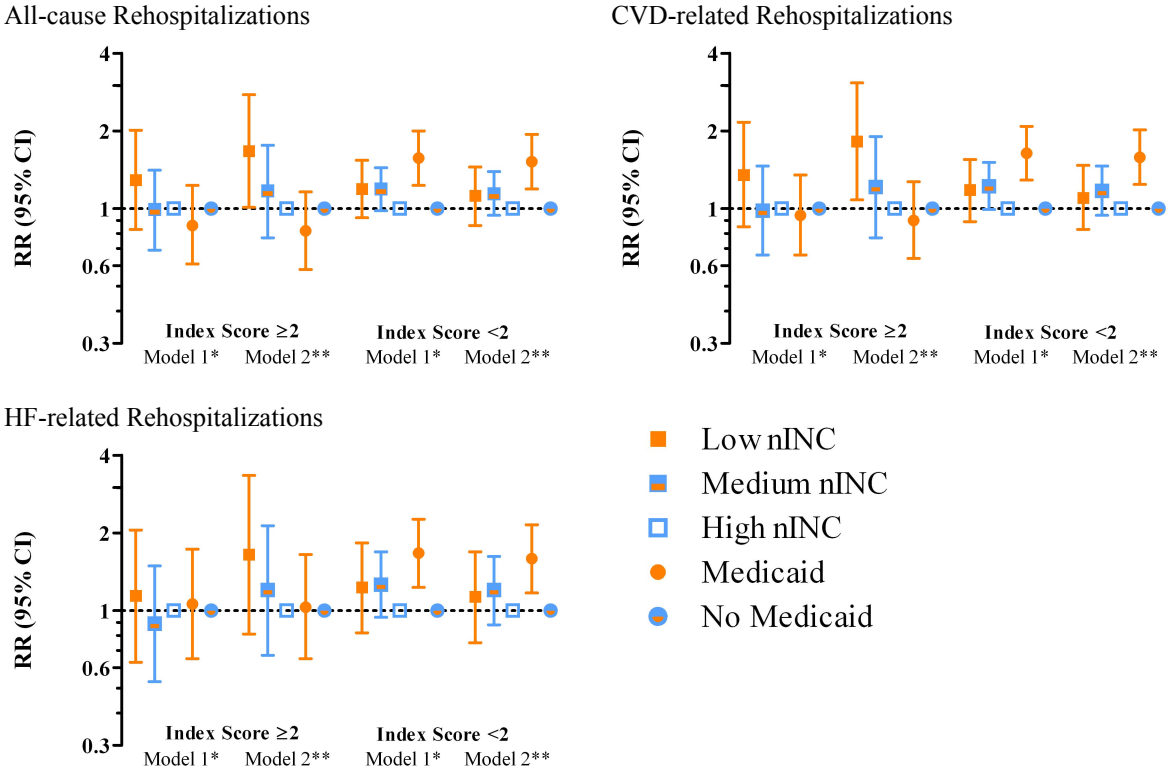
[a]nINC and Medicaid status plus race/study community, gender and age at index event
[b]Model 1 plus hypertension, body mass index, current smoker, current drinker and educational attainment

Of 1,342 participants with an incident HF hospitalization, 255 (19%) were not rehospitalized for any cause, while 318 (24%) were not rehospitalized for a CVD-related

cause and 590 (44%) were not rehospitalized for HF. All-cause rehospitalization rates per 100 person-years (95% CI) were 71.3 (63.3-80.4) for low nINC, 71.9 (64.5-80.2) for medium nINC, and 54.3 (47.7-61.7) for high nINC.

In models controlling for race/study community, gender, age at HF diagnosis, BMI, hypertension, educational attainment, receipt of Medicaid, alcohol use and smoking, participants with a higher burden of comorbidity living in low nINC areas had a higher risk of all-cause (1.67, 1.01-2.76) and CVD-related (1.82, 1.08-3.07) – but not HF-related (1.65, 0.81-3.34) – hospitalizations, compared to those with a high burden of comorbidity living in high nINC areas. Participants living in medium nINC areas at baseline did not have an elevated risk compared to participants living in high nINC areas, nor was there an nINC differential among participants with a low burden of comorbidity. Similar results were seen for CVD-related hospitalizations; however, no nINC effect in either strata of comorbidity burden was seen for HF-related hospitalizations, possibly due to relatively few events meeting the criteria for HF-related hospitalizations. Among participants with a low comorbidity burden, Medicaid recipients were at increased risk for all-cause hospitalizations. The observed results persisted for Medicaid recipients with a low comorbidity burden in analyses for CVD- and HF-related hospitalizations (**Figure 5.4**).

Figure 5.4. Rate ratios and 95% confidence intervals for rehospitalization among participants with an incident hospitalized heart failure event by type of rehospitalization, The ARIC study (1987-2004)



In our data, the Poisson models used for estimating rehospitalization rate ratios yielded a deviance statistic of close to four. Thus, over-dispersion was suggested. In response, we fit negative binomial models to the data. As expected, the point estimates of the rate ratios did not change, however, the confidence intervals widened with the application of the negative binomial model, reflecting the effect over-dispersion had on these data. Although the negative binomial estimates were less precise, the analyses accounting for over-dispersion did not change our interpretation of the results (data not shown).

In summary, accounting for all potential covariates, participants living in low nINC areas at baseline with a high burden of comorbidity were at greater risk for both

rehospitalization and death, as well as a higher rate of repeat hospitalizations, following an in-hospital HF diagnosis. Meanwhile, Medicaid recipients with fewer comorbidities had a significantly higher rate of repeat hospitalizations than participants in the same comorbidity category who were not Medicaid recipients. Additional adjustment for hospital type (teaching vs. non-teaching) did not change the results.

E. DISCUSSION

In this study, incident HF hospitalizations were more common among ARIC cohort participants of low and medium nINC compared to those living in high nINC areas at baseline. Further, low nINC participants with an elevated comorbidity index score at the time of the incident hospitalized HF event were rehospitalized at a higher rate than high nINC participants in the same comorbidity category. These findings were consistent with a review concluding that hospital admission rates increase with increased social deprivation (Blair et al., 2002). In addition, we found that participants had an increased hazard of rehospitalization, death and rehospitalization or death if they lived in a low nINC area at baseline and had a higher burden of comorbidity, compared to participants living in high nINC areas at baseline with a similar level of comorbidity.

Patients with limited neighborhood socioeconomic resources may not have adequate social support or access to primary care facilities necessary to manage HF out-of-hospital. Persons living in economically deprived areas may be less likely to have a primary care physician, and thus may seek care in-hospital for conditions commonly managed out-of-hospital. McAlister (2004) reported follow-up rates with primary care physicians were lowest among patients with high neighborhood socioeconomic deprivation (F. A. McAlister

et al., 2004). Fewer primary care visits may be an indication of higher hospital utilization rates among patients of lower nINC. A limitation of our study is that we are unable to take into account out-of-hospital management of HF, as outpatient records were not available for the time period under study. Future investigations in ARIC will, however, attempt to monitor the outpatient events related to HF.

Medicaid recipients without a high burden of comorbidity tended to have a higher hazard of first rehospitalization, and were rehospitalized more often than participants not receiving Medicaid. It is possible that the Medicaid recipients in this study with greater comorbidity were more likely to seek or be referred to care for symptom managment out-of-hospital and as a result did not require more frequent hospitalizations than non-Medicaid recipients with a high comorbidity burden. Conversely, the Medicaid recipients with fewer comorbidities in this study may not have been as aggressively managed in- or out-of- hospital, leading to a higher hazard of first rehospitalization following the index HF hospitalization.

Shorter median times from the index event to readmission among those living in low nINC areas appeared to be a strong influence on the combined rehospitalization/mortality endpoint, as low nINC was not a predictor for HF survival across levels of comorbidity in the ARIC study population. In particular, rehospitalization occurs more often and more quickly among participants living in low nINC areas, especially among those with more comorbidities identified during the incident hospitalized event. In general, patients with more comorbidity may require a greater number of treatments because they are sicker, more susceptible to severe HF, or experience acute exacerbations of the disease. Requiring more medical attention due to a high burden of comorbidity may serve to highlight the limited

resources available in low nINC areas, either for adequate self-care (Booth & Hux, 2003) or out-of-hospital management of disease.

Strengths of this study include a racially diverse population of men and women who were free of HF at baseline and followed from 1987 to 2004 in order to capture an incident HF hospitalization, subsequent hospitalizations and fatal events. Longer follow-up more adequately depicts the survival experience and clinical course of HF progression for the majority of patients diagnosed with this chronic disease. The index HF hospitalization was defined as the first mention of a *428* ICD-9 discharge code in the medical record, a technique used in extant studies of HF (Loehr et al., 2008). We acknowledge limitations inherent to this method of event identification, such as an inability to distinguish between acute and chronic HF events as well as not being able to determine the etiology of the incident hospitalized event. Although the identification of incident events via ICD-9 discharge codes does not capture outpatient events that may have occurred prior the incident hospitalized event, the distribution of hospitalizations among ARIC participants with incident hospitalized HF were similar to a recently published community-based report which ascertained incident HF cases from both outpatient and inpatient records (Dunlay et al., 2009).

In the context of increasing hospital discharges for HF and a consistently high rate of mortality from the syndrome, it is critical to identify social and economic neighborhood forces which impact HF rehospitalization or death in the presence of individual socioeconomic, demographic and comorbid factors. Differences by nINC in survival free from readmission or death post-incident HF hospitalization may have important implications for the management and treatment of HF patients (Chaix et al., 2007; Stjarne et al., 2006). It is likely that nINC in part determines the availability of health care resources in a

community, such as the proximity of neighborhood health clinics. Outpatient care is critical to the out-of-hospital monitoring of HF patients, and if less available in low nINC areas, may adversely affect the progression of HF among patients in these communities (G. Lee & Carrington, 2007). In this study, Medicaid recipients with a low burden of comorbidity were more likely to be admitted to the hospital following an incident hospitalized HF event. Whether or not these patients are adequately monitored on an outpatient basis remains unclear. Regardless, comorbidity burden appears to influence the association between nINC, Medicaid status and rehospitalization and death among HF patients.

VI. Socioeconomic Status and the Trajectory of Self-rated Health

A. ABSTRACT

Self-rated health (SRH) is thought to reflect both mental and physical health domains, and is assessed by asking individuals to objectively describe their health status. SRH is associated with disease incidence and subsequent mortality. Changes in SRH across an extended period of time in persons with different incident diseases are uncharacterized. SRH was assessed in the Atherosclerosis Risk in Communities (ARIC) study during annual telephone interviews over a median of 17.6 years of follow-up, and differences in SRH were determined by neighborhood median household income (nINC), which was derived from the 1990 US Census from participant addresses at study baseline (1987-1989). Individual quadratic growth models were used for repeated measures of SRH in persons who remained disease-free during follow-up (N=11,188), as well as among those who were diagnosed with myocardial infarction (MI; N=1,071), stroke (N=809), heart failure (HF; N=1,592) or lung cancer (N=433), and those who underwent a cardiac revascularization procedure (N=1,340) during follow-up. Among disease-free participants and across time, there was a trend for lowest mean SRH among persons living in low nINC areas and highest mean SRH among persons living in high nINC areas. Factors contributing to the decline in SRH over time included advanced age, lower educational attainment, smoking and obesity. Addressing factors related to poor SRH trajectories among patients pre- and post-incident disease may favorably affect health outcomes among patients regardless of type of disease.

B. INTRODUCTION

Self-rated health (SRH) is a commonly used measure of general health status, which is thought to reflect both mental and physical health domains (Singh-Manoux et al., 2006). SRH is typically obtained by asking individuals to objectively describe their health status on a four- to eight-point Likert scale (e.g., excellent, good, fair or poor)(Singh-Manoux et al., 2007). SRH is generally stable until age 50 years (McCullough & Laurenceau, 2004), and then declines with increasing age (McFadden et al., 2008). Low SRH is associated with adverse health outcomes, such as repeated hospitalizations (Kennedy et al., 2001) and mortality (Bardage, Isacson, & Pedersen, 2001; Wolinsky et al., 2008). Thus, it is hypothesized that low SRH may be able to predict a wide range of adverse health outcomes (Bardage et al., 2001).

Cross-sectional analyses of elderly persons demonstrate that living in disadvantaged neighborhoods, having low education and low household wealth is associated with self-reported poor health (Daponte-Codina et al., 2008; Kunst et al., 2005; Power et al., 1998; Wight et al., 2008). Furthermore, the association between neighborhood-level socioeconomic status (SES) and SRH remains after taking other individual-level measures - including measures of income, education and occupation - into account (Wight et al., 2008). Hypothesized mechanisms linking low SES with poor SRH may include an increase in allostatic load due to the stressors of low SES, and the availability of fewer resources in low SES areas to effectively manage such stress (Wight et al., 2008).

While many studies have investigated factors associated with current SRH (Daponte-Codina et al., 2008; McFadden et al., 2008; Wight et al., 2008) or a change in SRH (e.g.,

from baseline) (Wolinsky et al., 2008), few studies have reported the trajectory of repeated measures of SRH across a specified time period (P. Diehr et al., 2001). To our knowledge, research quantifying the trajectory of repeated measures of SRH among patients with incident disease by SES has not been undertaken, and may provide additional insight into the study of disease progression. Information regarding SRH trajectories that differ by SES could be used to develop interventions which prevent the loss of well-being associated with an incident disease diagnosis, with interventions tailored to address issues pertinent to the specific disease diagnosis.

C. METHODS

The participants of the Atherosclerosis Risk in Communities (ARIC) cohort were enrolled from four U.S. communities (Washington County, Maryland; Forsyth County, North Carolina; Jackson, Mississippi; and eight suburbs of Minneapolis, Minnesota) beginning in 1987 (White et al., 1996). ARIC study staff conducts annual follow-up by telephone to update address and contact information, and to assess overnight hospitalizations and changes in health status occurring since the last annual contact.

SRH was measured among 15,792 black and white men and women at baseline and at each annual follow-up (1987-2006) for a median of 17.6 (range 1-19) years using the question, "Over the past year, compared to other people your age, would you say that your health has been *excellent*, *good*, *fair* or *poor*?" SRH data are simple to collect (McFadden et al., 2008), yet may be difficult to interpret, since the SRH scale is not precisely ordinal and is based on a subjective opinion of one's health status. Thus, Diehr et al (2003) proposed a transformation based on data from the Cardiovascular Health Study to a scale from 100

(perfect health) to 0 (death). Diehr's transformation represents the probability of being healthy in the future, conditional on the current value of SRH (Paula Diehr & Patrick, 2003). Thus, we transformed SRH accordingly: 95 for *excellent*, 80 for *good*, 30 for *fair*, 15 for *poor*, and 0 for *death*.

Participants' baseline place of residence (1987-1989) was geocoded to the level of the census tract by a vendor with demonstrated accuracy, as described elsewhere (Whitsel et al., 2004). Neighborhood-level median household income (nINC) was obtained from the 1990 US Census and averaged across all ARIC study communities. Participants were assigned a tertile of nINC [low (<$24,777), medium ($24,777≤-<36,071) or high (≥$36,071)] based upon their address at baseline.

There were 276,200 total SRH observations for members of the cohort; 9,552 (3.4%) were missing. If an observation was missing, and there were complete SRH values for both the previous and subsequent year of follow-up, we imputed the missing observation by averaging the values from the previous and subsequent years. As a result, over half (N=5,140) of the missing observations were imputed. We assigned a zero for the missing value if it occurred during the year in which the cohort member died. In order to capture the SRH of the entire cohort across time, and not just that of the survivors, we included observations through contact year 19 for members lost to follow-up or who were deceased, and assigned a zero for each follow-up year which occurred after the cohort members' death.

Of the original 15,792 cohort members, 754 were excluded due to missing nINC (N=13,030 SRH observations), resulting in 263,170 SRH observations available for these analyses. We analyzed mean SRH at discrete time points and trajectories of SRH across time

among participants who were free of the selected diseases of interest as described below ("disease-free") at baseline and disease-free throughout follow-up (N=11,188), as well as among those disease-free at baseline and receiving a diagnosis of incident myocardial infarction (MI; N=1,071), stroke (N=809), heart failure (HF; N=1,592) or lung cancer (N=433), and those undergoing cardiac revascularization procedures (N=1,340) during follow-up. We assessed SRH data through the end of 2006, and incident events through the end of 2005, in order to give each cohort member at least one year of follow-up post-event.

For comparison purposes, each member of the disease-free group was assigned a random "event" date (P. Diehr et al., 2001). As a result, the pre-event and post-event trajectories from the incident disease groups could be compared to those of the group which remained healthy throughout follow-up, to determine if the SRH trajectories among the diseased differ from the trajectory of SRH that would be expected due to disease-free aging. With regard to differences by incident disease status, HF survival has been shown to be worse than other cardiovascular diseases and cancers, with the exception of lung cancer (Simon Stewart et al., 2001), and it remains unknown if SRH trajectories show similar trends.

Factors influencing pre- and post-event trajectories were of interest, as well as covariates which played a role in the decline of SRH over the follow-up period. Age (centered at 65 years) and age squared at the time of the annual follow-up contact were included in statistical models. Gender and race/study community were the additional demographic variables of interest. Health status and behavior variables assessed at baseline included body mass index (BMI), classified into normal (referent, <25 kg/m^2), overweight (25-<29.9 kg/m^2) or obese (≥ 29.9 kg/m^2); hypertension, present if systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or if taking hypertensive medication within the previous two weeks;

current drinker and current smoker. Educational attainment was assessed at baseline and categorized as less than 11 years, high school graduate, and greater than high school (referent). We accounted for period effects [1987-1992 (referent), 1993-1999 and 2000-2006] at each annual follow-up contact in order to capture secular trends (Rice et al., 2010) which may influence the nINC-SRH relationship, such as changes in health behaviors and disease treatments occurring in the ARIC communities over time. We used an indicator variable, accounting for the presence of disease (yes/no) at each annual follow-up, which represented the change in SRH from pre- to post-disease, while an interaction term (time*indicator variable) reflected the change in slope pre- to post-disease.

We regressed incident disease-specific SRH at each time point of interest (e.g., baseline; three, two, and one year prior to the event; event year; and one, two, three, four and five years post-event) on study covariates to generate estimated adjusted SRH values and standard errors (PROC GLM, SAS 9.1.3, Cary, NC). We used the change in adjusted SRH between the year of event and one year later to calculate how much of the decline in SRH post-event was due to death for each incident disease group. For example, we calculated the mean adjusted decline in SRH among participants who were alive one-year post event and divided that value by the mean adjusted decline in SRH among all participants (regardless of vital status). The proportion of decline in SRH post-event due to deaths was then one minus the aforementioned value.

If a relationship between nINC and SRH exists, it is feasible that nINC may influence the slope of decline in SRH over time depending on the type of incident health condition. Thus, we fit individual quadratic growth models separately to data by incident disease group, accounting for repeated measures of SRH (PROC MIXED, SAS 9.1.3, Cary, NC). Effect

measure modification of the nINC-SRH relationship was assessed (disease-free: $p_{interaction}<0.01$; other disease: $p_{interaction}<0.05$) by demographic, medical history and health behavior variables.

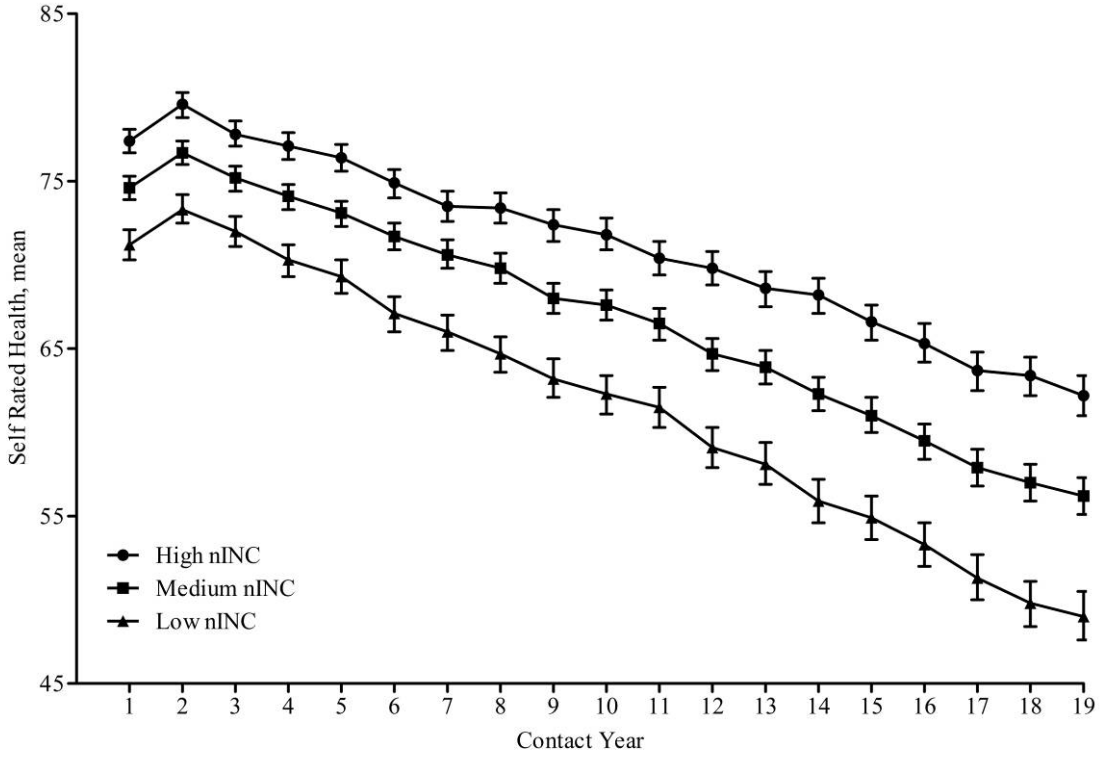
D. RESULTS

Disease-free participants were more likely to reside in high nINC areas (36.1%) at baseline (**Table 6.1**), be female (59.2%) and have greater than a high school education (37.7%). Among participants who were not disease-free over the course of follow-up, participants receiving a cardiac revascularization procedure were more likely to be male (67.3%). Stroke patients were more likely to be living in low nINC areas (43.8%) and heart failure patients were most likely to have less than a high school education (39.2%). **Figure 6.1** shows the relationship between nINC and SRH at each contact year, adjusted for age, race/study community and gender. SRH declined over time and overall by nINC, and there was a stepwise association between nINC and mean SRH, such that participants living in high nINC areas at baseline consistently reported higher SRH values, followed by those living in medium nINC areas, while participants living in low nINC areas at baseline rated their health as the lowest across the entire study period (**Figure 6.1**).

Table 6.1. Baseline characteristics of participants by incident disease status, The ARIC study (1987-2005)

	Disease-free N=11,188	Cardiac Revascularization Procedure N=1,340	Myocardial Infarction N=1,071	Lung Cancer N=433	Stroke N=809	Heart Failure N=1,592
Age, mean	54.2	55.7	56.0	57.5	54.7	57.1
nINC						
Low	29.5	21.8	25.8	31.6	43.8	42.6
Medium	34.4	44.5	40.0	40.2	29.0	33.3
High	36.1	33.7	34.2	28.2	27.2	24.1
Female	59.2	32.7	43.0	36.7	55.3	46.8
Race/Study Community						
Black/NC	3.1	2.7	2.8	3.2	3.6	3.3
Black/MS	22.7	10.6	24.4	19.2	39.9	31.0
White/NC	22.4	29.2	24.3	26.1	17.1	19.8
White/MN	27.4	27.5	21.9	24.5	17.2	17.6
White/MD	24.4	30.0	26.6	27.0	22.2	28.3
Hypertensive	31.2	40.2	48.6	37.9	42.3	54.0
Overweight or obese	65.0	65.9	74.8	55.9	70.2	78.1
Current smoker	23.0	30.5	37.4	65.8	28.1	37.0
Current drinker	57.3	57.1	49.6	64.0	48.7	45.4
Educational Attainment						
Less than HS	21.0	23.5	32.6	33.5	27.9	39.2
HS or equivalent	41.1	42.7	37.9	43.0	42.4	36.9
Greater than HS	37.7	33.7	29.4	23.5	29.4	23.6

Figure 6.1. The relationship between nINC and SRH across all contact years of follow up for the entire cohort, The ARIC study (1987-2006)

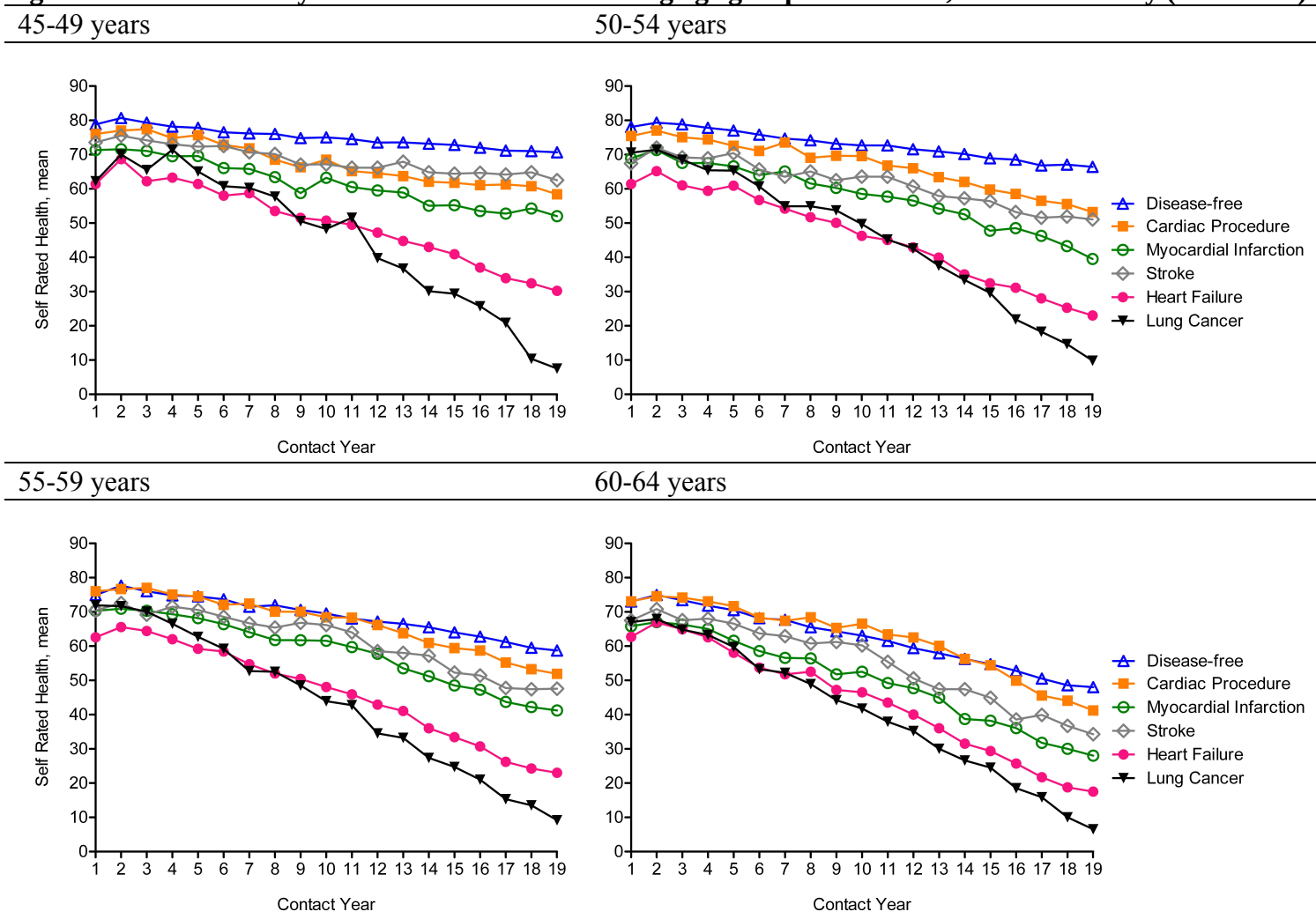


Adjusted for age, race/study community and gender

Each type of incident disease was treated separately, thus it was possible for cohort participants to belong to more than one incident disease group, with the exception of disease-free participants. The largest overlap occurred between incident MI and cardiac revascularization procedure, which shared 12% of participants. All other types of incident disease co-occurred at either a rate of 5% (e.g., HF and cardiac revascularization procedure, and HF and MI) or ≤1% (data not shown). **Figure 6.2** shows the impact of baseline age on the trajectory of mean SRH across all contact years by incident disease status. Participants aged 60-64 years at baseline tended to report lower SRH and demonstrate a steeper decline in SRH across study follow-up as compared to participants aged 45-49 years at baseline,

regardless of incident disease status (**Figure 6.2**). Those with lung cancer had the lowest SRH across all age groups, followed by those with HF.

Figure 6.2. Mean SRH by incident disease status among age groups at baseline, The ARIC study (1987-2006)



At baseline, 33.2% of participants reported *excellent*, 46.8% *good*, 16.6% *fair* and 3.4% *poor* SRH. The internal validity of the SRH measure in this cohort was high, as participants reporting *excellent* health at baseline were least likely (and those reporting *poor* health at baseline were most likely) to be hypertensive, overweight/obese or to be deceased by the end of follow-up (**Table 6.2**).

Table 6.2. Percentage of participants reporting a given SRH at baseline who had existing comorbid disease or had died by the end of follow-up: The ARIC Study (1987-2005)

SRH at baseline		Hypertensive	Overweight or obese	Deceased by the end of follow-up
Excellent	33.2	18.7	58.3	11.2
Good	46.8	36.7	68.8	18.9
Fair	16.6	54.7	77.8	34.7
Poor	3.4	66.1	75.2	55.8

Adjusting for age, race/study community, gender, hypertensive status, BMI, current smoking, current drinking, educational attainment and period effects, mean SRH was highest at baseline, pre-event, post-event and across entire follow-up for disease-free participants. Among disease-free participants and across time points, there was a trend for lowest mean SRH among persons living in low nINC areas and highest mean SRH among persons living in high nINC areas (**Table 6.3**). This trend did not hold for all five incident disease types across all time points. Among participants with a cardiac revascularization procedure during follow-up, low nINC was associated with the lowest mean SRH pre-event, post-event and overall, but not at baseline. Low nINC was also associated with low mean SRH across the entire follow-up (overall) for MI and lung cancer, but not for stroke or HF.

Table 6.3. Mean SRH at selected time points during follow-up by incident disease status, The ARIC study (1987-2006)

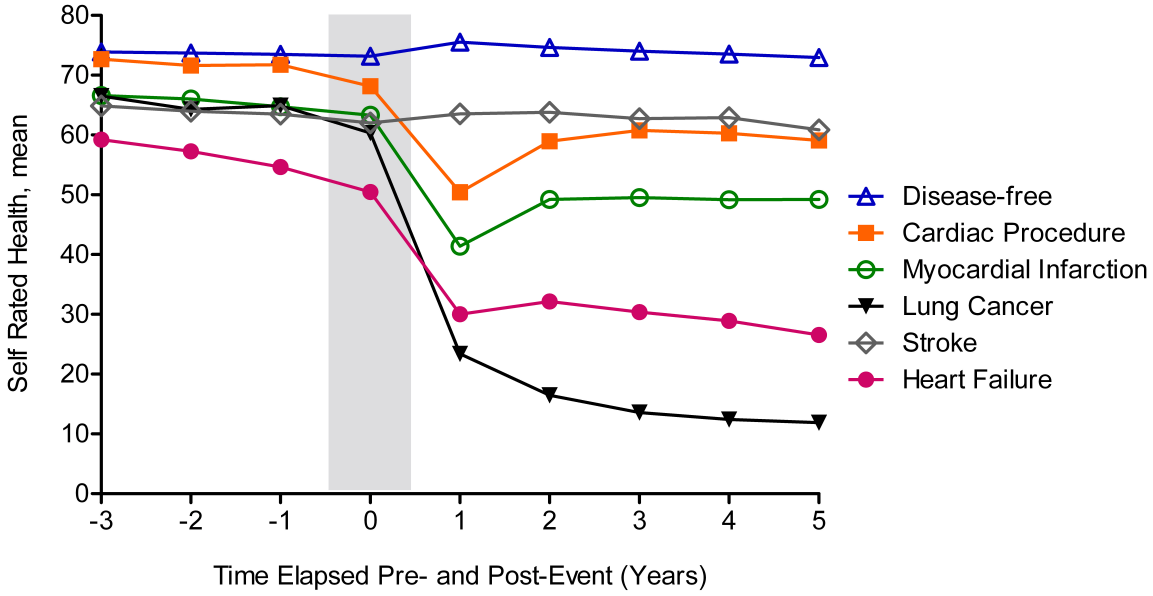
	nINC	Baseline	Pre-disease	Post-disease	Overall
Disease-free	Low	75.3 (74.4-76.3)	71.6 (71.2-72.0)	70.2 (69.7-70.7)	68.6 (68.3-68.9)
	Medium	76.7 (75.9-77.4)	74.2 (73.9-74.5)	71.8 (71.4-72.1)	70.6 (70.4-70.8)
	High	77.6 (76.8-78.3)	75.4 (75.1-75.8)	73.5 (73.2-73.9)	72.5 (72.2-72.7)
Cardiac Revascularization Procedure	Low	74.5 (71.5-77.6)	70.5 (69.5-71.5)	50.1 (48.6-51.6)	61.3 (60.4-62.2)
	Medium	75.4 (73.5-77.2)	75.2 (74.6-75.8)	55.5 (54.5-56.4)	67.0 (66.4-67.5)
	High	75.3 (73.0-77.5)	74.3 (73.6-75.0)	58.3 (57.2-59.5)	67.7 (67.0-68.3)
Myocardial Infarction	Low	68.1 (64.7-71.4)	66.1 (65.0-67.3)	39.4 (37.8-40.9)	52.1 (51.1-53.1)
	Medium	70.7 (68.1-73.4)	69.6 (68.8-70.5)	48.0 (46.8-49.2)	60.0 (59.2-60.7)
	High	68.0 (64.6-71.4)	67.6 (66.4-68.7)	47.1 (45.5-48.7)	58.4 (57.4-59.4)
Lung Cancer	Low	67.9 (62.6-73.2)	67.1 (65.4-68.9)	8.1 (6.5-9.8)	40.8 (39.0-42.6)
	Medium	69.3 (65.2-73.4)	69.0 (67.7-70.2)	9.9 (8.5-11.3)	44.8 (43.4-46.2)
	High	69.1 (63.9-74.3)	67.7 (66.0-69.3)	15.6 (13.9-17.4)	44.4 (42.6-46.2)
Stroke	Low	72.9 (69.6-76.2)	61.8 (60.6-63.1)	65.4 (63.9-66.9)	63.1 (62.2-64.1)
	Medium	66.9 (63.1-70.5)	67.4 (66.1-68.8)	53.2 (51.5-54.8)	61.5 (60.4-62.5)
	High	68.7 (64.9-72.5)	64.4 (62.9-65.9)	58.3 (56.6-59.9)	61.7 (60.6-62.8)
Heart Failure	Low	62.6 (60.0-65.1)	61.8 (60.9-62.6)	24.6 (23.6-25.7)	45.5 (44.7-46.3)
	Medium	63.1 (60.5-65.6)	61.9 (61.1-62.7)	26.0 (24.9-27.1)	47.4 (46.7-48.2)
	High	60.9 (57.7-64.1)	61.5 (60.5-62.5)	23.8 (22.5-25.2)	45.7 (44.8-46.7)

Adjusted for age, race/study community, gender, hypertensive status, body mass index, current smoking, current drinking, educational attainment and period effects

Figure 6.3 shows mean SRH by type of incident disease pre- and post-event, adjusting for age, race/study community, gender, hypertensive status, BMI, current smoking, current drinking, educational attainment and period effects. Average SRH three years prior to the incident event was highest among disease-free participants (73.9) and lowest among those developing HF (59.2). Between three years pre-event and the event year, the smallest average decline in SRH occurred among disease-free individuals (-1.4), while the largest average decline occurred among those developing HF (-8.2). Large declines in SRH were seen during the one year following the event among MI, cardiac revascularization procedure, lung cancer and HF patients. The percent of the decline in SRH due to death among these patients was 16%, 8%, 24% and 32%, respectively. A gradual increase in SRH post-event

was seen among participants surviving events that did not have as high of a burden of mortality as HF and lung cancer (**Figure 6.3**).

Figure 6.3. Trajectory of SRH pre- and post-event, The ARIC study (1987-2006)



Adjusted for nINC, age, race/study community, gender, hypertensive status, body mass index, current smoking, current drinking, educational attainment and period effects

After fitting individual quadratic growth models separately to data by incident disease group, and controlling for all available covariates, advancing age, lower educational attainment, current smoking and obesity were predictors of the decline in SRH over time regardless of type of incident disease (**Table 6.4**). For all incident disease types except lung cancer, being hypertensive contributed to significant declines in SRH over time. Among disease-free participants, as well as participants undergoing cardiac revascularization procedures or with MI, living in low nINC areas at baseline was a predictor of SRH decline. Notable among disease-free participants was a significant interaction between nINC and educational attainment, indicating that the combination of low nINC and lower educational

attainment conferred a statistically significant excess risk of an additional decrease in the trajectory of SRH over time. Statistically significant declines in SRH occurred among participants pre- and post- event, except among those experiencing a stroke. Meanwhile, statistically significant changes in slope pre- and post- event occurred for all incident disease types.

Table 6.4. Predictors of declines in SRH over time by incident disease status: The ARIC Study (1987-2006)

	Disease-free N=11,188	Cardiac Revascularization Procedure N=1,340	Myocardial Infarction N=1,071	Lung Cancer N=433	Stroke N=809	Heart Failure N=1,592
Intercept	87.7 (0.8)*	84.8 (2.2)*	78.5 (2.9)*	79.7 (4.6)*	81.3 (3.4)*	71.2 (2.5)*
Age, centered at 65	-0.5 (0.04)*	-0.3 (0.1)*	-0.6 (0.1)*	-0.3 (0.2)	-0.9 (0.1)*	-0.3 (0.1)*
Age^2	-0.03 (0.002)*	-0.02 (0.004)*	-0.03 (0.005)*	-0.02 (0.01)*	-0.03 (0.01)*	-0.03 (0.005)*
nINC (vs. High)						
Low	-2.3 (0.8)*	-5.2 (1.7)*	-5.0 (2.3)*	2.0 (5.0)	1.8 (2.1)	-0.04 (1.6)
Medium	-1.2 (0.6)*	-0.9 (1.3)	1.2 (1.9)	6.2 (3.8)	-0.6 (1.9)	0.5 (1.4)
Female (vs. male)	-1.0 (0.3)*	-3.7 (1.0)*	-1.9 (1.2)	-0.6 (1.7)	1.7 (1.3)	0.01 (1.0)
Race/Study Community (vs. White/MD)						
Black/NC	-6.5 (0.9)*	-1.3 (2.8)	-7.4 (3.5)*	-6.1 (5.3)	-9.1 (3.7)*	-8.0 (2.8)*
Black/MS	-8.7 (0.6)*	-3.7 (1.8)*	-6.1 (2.0)*	-5.5 (2.9)	-10.7 (2.2)*	-7.5 (1.6)*
White/NC	-0.8 (0.4)	-0.6 (1.1)	0.1 (1.6)	1.9 (2.2)	-2.1 (2.1)	-3.6 (1.4)*
White/MN	0.1 (0.5)	2.1 (1.3)	4.6 (1.8)*	1.6 (2.6)	2.6 (2.2)	2.4 (1.6)
Hypertensive	-4.9 (0.3)*	-4.4 (0.9)*	-5.6 (1.2)*	-2.4 (1.8)	-7.9 (1.4)*	-4.2 (1.0)*
BMI (vs. Normal)						
Obese	-4.8 (0.4)*	-6.8 (1.2)*	-5.8 (1.5)*	-5.4 (2.1)*	-7.1 (1.7)*	-2.8 (1.3)*
Overweight	-0.7 (0.3)*	-2.8 (1.1)*	-1.3 (1.4)	-1.1 (1.9)	-3.6 (1.6)*	0.9 (1.3)
Current smoker	-4.0 (0.4)*	-3.8 (1.0)*	-4.2 (1.2)*	-4.7 (1.8)*	-7.8 (1.4)*	-3.8 (1.0)*
Current drinker	1.6 (0.3)*	3.6 (0.9)*	3.4 (1.2)*	0.9 (1.8)	2.5 (1.4)	2.8 (1.0)*
Educational Attainment (vs. Greater than HS)						
Less than HS	-9.5 (1.0)*	-9.7 (1.3)*	-10.3 (1.5)*	-11.5 (5.2)*	-12.9 (1.7)*	-9.5 (1.3)*
HS or equivalent	-3.2 (0.5)*	-3.4 (1.0)*	-5.0 (1.3)*	4.7 (3.2)	-6.0 (1.5)*	-3.9 (1.2)*

	Disease-free N=11,188	Cardiac Revascularization Procedure N=1,340	Myocardial Infarction N=1,071	Lung Cancer N=433	Stroke N=809	Heart Failure N=1,592
Contact year	-0.3 (0.04)*	-0.2 (0.1)	0.1 (0.1)	-0.6 (0.2)*	0.1 (0.2)	-0.4 (0.1)*
Disease status	-1.7 (0.3)*	-14.9 (1.1)*	-19.5 (1.2)*	-44.7 (2.4)*	-4.8 (1.3)*	-26.3 (1.2)*
1987-1992 (vs. 2000-2006)	-0.6 (0.4)	0.9 (1.1)	1.4 (1.5)	-1.3 (2.1)	3.0 (1.3)*	5.0 (1.0)*
1993-1999 (vs. 2000-2006)	-0.01 (0.2)	0.04 (0.7)	-0.03 (1.0)	-0.8 (1.3)	2.3 (0.7)*	3.2 (0.6)*
Age, centered at 65*1987-1992	-0.1 (0.05)*	NS	NS	NS	0.03 (0.2)	NS
Age, centered at 65*1993-1999	0.05 (0.03)	NS	NS	NS	0.3 (0.1)*	NS
Low nINC*Less than HS	-3.9 (1.2)*	NS	NS	1.9 (6.8)	NS	NS
Low nINC*HS or equivalent	-2.7 (0.8)*	NS	NS	-12.4 (5.6)*	NS	NS
Medium nINC*Less than HS	-1.5 (1.2)	NS	NS	-4.6 (6.3)	NS	NS
Medium nINC*HS or equivalent	-0.3 (0.8)	NS	NS	-8.2 (4.6)	NS	NS
Low nINC*1987-1992	2.0 (0.4)*	1.8 (1.3)	3.3 (1.6)*	NS	NS	NS
Low nINC*1993-1999	0.6 (0.3)	-0.3 (1.0)	2.1 (1.2)	NS	NS	NS
Medium nINC*1987-1992	0.4 (0.4)	0.5 (1.1)	-0.6 (1.6)	NS	NS	NS
Medium nINC*1993-1999	0.3 (0.3)	1.5 (0.8)*	1.0 (1.2)	NS	NS	NS
Contact year*Disease status	0.2 (0.03)*	0.4 (0.1)*	-0.6 (0.1)*	0.6 (0.2)*	0.2 (0.1)	0.8 (0.1)*

Significant predictors ($p<0.05$) are indicated with an (*)
NS = Interaction Not Significant for this model

E. DISCUSSION

To our knowledge, this is the first study to characterize trajectories of change in SRH status in assessing chronic disease burden pre- and post- incident disease diagnosis. Values of SRH tended to be lower at baseline and declined at a greater rate prior to the disease occurrence among participants who were disease-free at baseline but developed a disease over the course of follow-up compared to healthy members of the cohort. The largest pre-event decline occurred in the HF group. A positive stepwise assocation between nINC and SRH persisted across 19 years of followup of the entire cohort, regardless of incident disease status. While nINC contributed to the decline in SRH among members of the cohort with selected types of incident disease, it was not a contributing factor to SRH decline over time for all participants, unlike age, educational attainment, current smoking and obesity. With exception of lung cancer, being hypertensive contributed to significant declines in SRH over time.

In order to get an accurate picture of the trajectory of SRH among members of a cohort, it was important to account for death in the analyses. For example, if only live participants are considered during follow-up, SRH may have been shown to improve after a sentinel health event, since the sickest patients (i.e. those with *fair* or *poor* SRH) have disproportionately died (Paula Diehr & Patrick, 2003). Similarly, had we attributed a zero to the participants' year of death, but counted SRH values as missing thereafter, we would have tracked the post-event SRH trajectories of the disease survivors, and ignored the experience of the entire cohort.

Trends in SRH differ for different types of incident disease. Previous studies have shown a decline in health status pre-event for diseases such as cancer, MI and HF, as well as a relationship between health-related quality of life and the risk of hospital readmission or death post-event (P. Diehr et al., 2001; Rodriguez-Artalejo et al., 2005). The steep decline in SRH post-event, followed by a leveling-off period, has been noted in other studies (P. Diehr et al., 2001). This phenomenon is at least in part due to the fact that all participants experiencing an incident event had to be alive prior to the event, after which they could die. As described in the results section, the percent of decline during the first year post-event varied by type of incident disease, with a high proportion of deaths affecting the lung cancer and HF groups the most and cardiac revascularization and MI patients the least.

Strengths of our study include a large number of SRH observations, due to nearly 20 years of annual cohort follow-up. We imputed SRH values if there were SRH values immediately prior to or following the missing value, allowing for a more complete picture of SRH across time. In addition, due to the thorough medical history obtained at baseline, we excluded participants with prevalent disease from study, thus restricting our analysis to incident events only. Our incident disease-specific results are consistent with an Israeli study which reported poor income, low education and obesity as independent predictors of a decline in SRH among MI patients (Gerber, Benyamini, Goldbourt, Drory, & for the Israel Study Group on First Acute Myocardial, 2009).

SRH is a good indicator of overall health status, however, multiple measurements of other subjective health indicators were not collected annually from participants. Thus, the extent to which a poor SRH rating was associated with poor physical health, mental health, functional status or a combination of these or other measures, such as positive or negative

affect (Winter, Lawton, Langston, Ruckdeschel, & Sando, 2007), cannot be ascertained from these data. Better functional status, for example, may improve one's ability to perform disease self-management techniques, which has been shown to have a positive impact on health status of HF patients (Suwanno, Petpichetchian, Riegel, & Issaramalai, 2009). In addition, there is evidence that different pathways may link SES to distinct domains of health status (Barbareschi, Sanderman, Kempen, & Ranchor, 2009).

Repeated measures data provide additional insight into the study of disease progression. In this study, significant predictors of the decline in SRH over a nearly 20-year period included age, educational attainment, current smoking and obesity. As SRH is associated with subsequent risk of morbidity and mortality, addressing factors related to poor SRH trajectories among patients pre- and post-incident disease may favorably affect health outcomes among patients regardless of type of incident disease.

VII. CONCLUSIONS AND PUBLIC HEALTH IMPLICATIONS

Rehospitalization and Mortality

In this study, incident HF hospitalizations were more common among ARIC cohort participants of low and medium nINC compared to those living in high nINC areas at baseline. Further, low nINC participants with an elevated comorbidity index score at the time of the incident hospitalized HF event were rehospitalized at a higher rate than high nINC participants in the same comorbidity category. These findings were consistent with a review concluding that hospital admission rates increase with increased social deprivation (Blair et al., 2002). In addition, we found that participants had an increased hazard of rehospitalization, death and rehospitalization or death if they lived in a low nINC area at baseline and had a higher burden of comorbidity, compared to participants living in high nINC areas at baseline with a similar level of comorbidity.

Patients with limited neighborhood socioeconomic resources may not have adequate social support or access to primary care facilities necessary to manage HF out-of-hospital. Persons living in economically deprived areas may be less likely to have a primary care physician, and thus may seek care in-hospital for conditions commonly managed out-of-hospital. McAlister (2004) reported follow-up rates with primary care physicians were lowest among patients with high neighborhood socioeconomic deprivation (F. A. McAlister et al., 2004). Fewer primary care visits may be an indication of higher hospital utilization rates among patients of lower nINC. A limitation of our study is that we are unable to take

into account out-of-hospital management of HF, as outpatient records were not available for the time period under study. Future investigations in ARIC will, however, attempt to monitor the outpatient events related to HF.

Medicaid recipients without a high burden of comorbidity tended to have a higher hazard of first rehospitalization, and were rehospitalized more often than participants not receiving Medicaid. It is possible that the Medicaid recipients in this study with greater comorbidity were more likely to seek or be referred to care for symptom managment out-of-hospital and as a result did not require more frequent hospitalizations than non-Medicaid recipients with a high comorbidity burden. Conversely, the Medicaid recipients with fewer comorbidities in this study may not have been as aggressively managed in- or out-of- hospital, leading to a higher hazard of first rehospitalization following the index HF hospitalization.

Shorter median times from the index event to readmission among those living in low nINC areas appeared to be a strong influence on the combined rehospitalization/mortality endpoint, as low nINC was not a predictor for HF survival across levels of comorbidity in the ARIC study population. In particular, rehospitalization occurs more often and more quickly among participants living in low nINC areas, especially among those with more comorbidities identified during the incident hospitalized event. In general, patients with more comorbidity may require a greater number of treatments because they are sicker, more susceptible to severe HF, or experience acute exacerbations of the disease. Requiring more medical attention due to a high burden of comorbidity may serve to highlight the limited resources available in low nINC areas, either for adequate self-care (Booth & Hux, 2003) or out-of-hospital management of disease.

Strengths of this study include a racially diverse population of men and women who were free of HF at baseline and followed from 1987 to 2004 in order to capture an incident HF hospitalization, subsequent hospitalizations and fatal events. Longer follow-up more adequately depicts the survival experience and clinical course of HF progression for the majority of patients diagnosed with this chronic disease. The index HF hospitalization was defined as the first mention of a *428* ICD-9 discharge code in the medical record, a technique used in extant studies of HF (Loehr et al., 2008). We acknowledge limitations inherent to this method of event identification, such as an inability to distinguish between acute and chronic HF events as well as not being able to determine the etiology of the incident hospitalized event. Although the identification of incident events via ICD-9 discharge codes does not capture outpatient events that may have occurred prior the incident hospitalized event, the distribution of hospitalizations among ARIC participants with incident hospitalized HF were similar to a recently published community-based report which ascertained incident HF cases from both outpatient and inpatient records (Dunlay et al., 2009).

In the context of increasing hospital discharges for HF and a consistently high rate of mortality from the syndrome, it is critical to identify social and economic neighborhood forces which impact HF rehospitalization or death in the presence of individual socioeconomic, demographic and comorbid factors. Differences by nINC in survival free from readmission or death post-incident HF hospitalization may have important implications for the management and treatment of HF patients (Chaix et al., 2007; Stjarne et al., 2006). It is likely that nINC in part determines the availability of health care resources in a community, such as the proximity of neighborhood health clinics. Outpatient care is critical to the out-of-hospital monitoring of HF patients, and if less available in low nINC areas, may

adversely affect the progression of HF among patients in these communities (G. Lee & Carrington, 2007). In this study, Medicaid recipients with a low burden of comorbidity were more likely to be admitted to the hospital following an incident hospitalized HF event. Whether or not these patients are adequately monitored on an outpatient basis remains unclear. Regardless, comorbidity burden appears to influence the association between nINC, Medicaid status and rehospitalization and death among HF patients.

There are concerns regarding the validity of using discharge diagnosis codes in diagnosing HF. The true number of HF cases or hospitalizations can be underestimated, for example, if cases are identified by only using primary, not secondary, discharge diagnosis criteria. In contrast, the absolute number of HF hospitalizations can be overestimated if the target diagnosis code is carried over from the incident hospitalization even if subsequent hospitalizations are not due to HF decompensation. As a result, it is suggested that hospital discharge data is not adequate to confirm the accuracy of a HF diagnosis, and may not be sufficient to verify the existence of comorbid illnesses (J.G.F Cleland et al., 2003).

Despite the aforementioned concerns, it is a common approach for epidemiologic researchers to use ICD-9-CM codes to identify HF cases. From a review of studies which incorporated hospitalized HF events, ICD-9-CM code 428 was the most consistently used code to identify hospitalized HF events (**Table 7.1**). The validity of using discharge diagnosis codes to identify HF hospitalizations is addressed by measures of sensitivity, specificity, as well as positive and negative predictive values. In assessing the validity of HF diagnosis codes in the primary or secondary position, Goff et al. (2000) found that the net effect of HF event misclassification resulted in an underestimation of hospitalizations attributable to acute HF (Goff et al., 2000). The authors investigated three different

algorithms for diagnosing HF in the Corpus Christi Heart Project, using a gold standard comprised of physician-diagnosed acute congestive HF or radiographic evidence of pulmonary edema for validation of HF. Three ICD-9-CM code-based algorithms were compared: (1) 428.x only, (2) 428.x or 402.x and (3) any HF-related ICD-9-CM code. Results showed the sensitivity of ICD-9-CM codes associated with HF ranged from approximately 63% to 67%, which indicated that nearly one-third of the patients studied who met criteria for a HF diagnosis were not appropriately diagnosed as having HF. Specificity was consistently greater than 92%, and positive predictive values ranged from 77% to nearly 84%, and the negative predictive value averaged 88%.

Table 7.1. Discharge codes commonly used in epidemiologic studies to identify heart failure

ICD-9-CM Codes	Study Population	Author
402.x1 404.x3 428.xx	5% sample of Medicare beneficiaries (n=622,789, 1994-2003)	Curtis LH (Curtis et al., 2008)
402.x 404.x 428.x	National Hospital Discharge Survey (1979-2004)	Fang J (Fang et al., 2008)
402.x 404.x 428.x	ADHERE (2001-2003, n=85,617) and update (2001-2004, n=105,388)	Galvao M (M. Galvao & ADHERE Scientific Advisory Committee (SAC) Investigators, 2005; Marie Galvao et al., 2006)
398.91 402.01, 402.11, 402.91 428.x	ANCHOR (1996-2002, n=59,772)	Go AS (Go et al., 2006)
428.x	Death certificates in state vital statistics offices (1980-1995)	Haldeman GA (CDC, 1998)
428.x	Canadian Institute for Health Information (n=38,702, 1994-1997)	Jong P (Jong et al., 2002)
402.9 428.0, 428.1, 428.9	Scotland national database linked with discharge and mortality data (n=12,640, 1992)	Khand AU (Khand et al., 2001)
425.4, 425.5, 425.9 428.0, 428.1, 428.9	Scotland (n=547, 1986-1995)	MacIntyre K (MacIntyre et al., 2000)
428.x	Rochester, MN (n=6,076, 1987-2001)	Owan TE (Owan et al., 2006)
402.01, 402.11, 402.91 404.01, 404.03, 404.11, 404.13, 404.91, 404.93 428.0, 428.1, 428.9	New York State (n=42,731, 1995)	Philbin EF (Philbin et al., 2001; Philbin & DiSalvo, 1999)
402.01, 402.11, 402.91 404.01, 404.91 428.x	National Heart Failure Project, Medicare sample (n=30,996, 1998-1999) and (n=53,640, 1998-1999 and 2000-2001)	Rathore SS (Rathore et al., 2005; Rathore et al., 2006) Smith GL (Smith et al., 2005)
398.91 402.01, 402.11, 402.91 425.x 428.x 997.1	Cardiovascular Health Study (n=5,888, 1989-2000)	Schellenbaum GD (Schellenbaum et al., 2006)

Further, it is reported that the majority of HF diagnoses are made in the hospital (Blackledge et al., 2003; Cowie et al., 2002). A community-based cohort study carried out in Olmsted County, Minnesota suggests that as hospitalization rates stabilize, the hospitalized burden of HF cases may shift to its management in the outpatient setting. Roger et al. reported 42% of HF cases were diagnosed in the outpatient setting in Olmsted County,

Minnesota. While nearly three-fourths of the cases diagnosed out-of-hospital were hospitalized within 1.7 years, 26% were never hospitalized (Roger et al., 2004).

Self-Rated Health

To our knowledge, this is the first study to characterize trajectories of change in SRH status in assessing chronic disease burden pre- and post- incident disease diagnosis. Values of SRH tended to be lower at baseline and declined at a greater rate prior to the disease occurrence among participants who were disease-free at baseline but developed a disease over the course of follow-up compared to healthy members of the cohort. The largest pre-event decline occurred in the HF group. A positive stepwise assocation between nINC and SRH persisted across 19 years of followup of the entire cohort, regardless of incident disease status. While nINC contributed to the decline in SRH among members of the cohort with selected types of incident disease, it was not a contributing factor to SRH decline over time for all participants, unlike age, educational attainment, current smoking and obesity. With exception of lung cancer, being hypertensive contributed to significant declines in SRH over time.

In order to get an accurate picture of the trajectory of SRH among members of a cohort, it was important to account for death in the analyses. For example, if only live participants are considered during follow-up, SRH may have been shown to improve after a sentinel health event, since the sickest patients (i.e. those with *fair* or *poor* SRH) have disproportionately died (Paula Diehr & Patrick, 2003). Similarly, had we attributed a zero to the participants' year of death, but counted SRH values as missing thereafter, we would have

tracked the post-event SRH trajectories of the disease survivors, and ignored the experience of the entire cohort.

Trends in SRH differ for different types of incident disease. Previous studies have shown a decline in health status pre-event for diseases such as cancer, MI and HF, as well as a relationship between health-related quality of life and the risk of hospital readmission or death post-event (P. Diehr et al., 2001; Rodriguez-Artalejo et al., 2005). The steep decline in SRH post-event, followed by a leveling-off period, has been noted in other studies (P. Diehr et al., 2001). This phenomenon is at least in part due to the fact that all participants experiencing an incident event had to be alive prior to the event, after which they could die. As described in the results section, the percent of decline during the first year post-event varied by type of incident disease, with a high proportion of deaths affecting the lung cancer and HF groups the most and cardiac revascularization and MI patients the least.

Strengths of our study include a large number of SRH observations, due to nearly 20 years of annual cohort follow-up. We imputed SRH values if there were SRH values immediately prior to or following the missing value, allowing for a more complete picture of SRH across time. In addition, due to the thorough medical history obtained at baseline, we excluded participants with prevalent disease from study, thus restricting our analysis to incident events only. Our incident disease-specific results are consistent with an Israeli study which reported poor income, low education and obesity as independent predictors of a decline in SRH among MI patients (Gerber et al., 2009).

SRH is a good indicator of overall health status, however, multiple measurements of other subjective health indicators were not collected annually from participants. Thus, the

extent to which a poor SRH rating was associated with poor physical health, mental health, functional status or a combination of these or other measures, such as positive or negative affect (Winter et al., 2007), cannot be ascertained from these data. Better functional status, for example, may improve one's ability to perform disease self-management techniques, which has been shown to have a positive impact on health status of HF patients (Suwanno et al., 2009). In addition, there is evidence that different pathways may link SES to distinct domains of health status (Barbareschi et al., 2009).

Repeated measures data provide additional insight into the study of disease progression. In this study, significant predictors of the decline in SRH over a nearly 20-year period included age, educational attainment, current smoking and obesity. As SRH is associated with subsequent risk of morbidity and mortality, addressing factors related to poor SRH trajectories among patients pre- and post-incident disease may favorably affect health outcomes among patients regardless of type of incident disease.

Public Health Implications

Extant studies of the social determinants of CHD conclude that low SES results in a higher incidence of HF compared to high SES. The current work implicates neighborhood-level SES in the progression of HF, as defined as rehospitalization and mortality. Specifically, patients with a high burden of comorbidity living in low nINC areas have a higher risk of rehospitalization and death compared to patients with a high burden of comorbidity living in high nINC areas. As a result, primary prevention efforts targeting HF incidence and comorbid conditions in low nINC areas are warranted, as are secondary

prevention efforts which are focused on effective outpatient management of HF patients living in low nINC areas.

It is likely that repeat hospitalizations and early mortality among HF patients from lower SES neighborhoods is in part due to inadequate outpatient management of HF. Primary prevention efforts in low nINC areas may serve to create an awareness of risk factors for CHD and to promote healthy behaviors in communities. Secondary prevention efforts, including providing access to outpatient management of HF in poor communities, may help alleviate patient suffering and the rising costs of inpatient visits due to HF and the associated comorbid illnesses.

Meanwhile, the current study found a more rapid decline in SRH among HF and lung cancer patients compared to patients with other types of incident disease. Influential factors in the decline in SRH among HF patients included low educational attainment, advanced age, hypertension, smoking and obesity. In the presence of these factors, low nINC did not exert a negative influence on the progression of SRH among HF patients. Given that poor SRH is predictive of future adverse health outcomes, such as rehospitalization and death, factors influencing significant declines in SRH, such as hypertension, smoking and obesity, should be addressed with primary and secondary prevention efforts in order to slow the decline of SRH. It remains unknown how low educational attainment adversely affects SRH. One hypothesis is that having a low educational status may cause an individual to perceive their health status differently in terms of how optimistic they may be in light of potential health problems. An alternative hypothesis is that persons with a low educational status may not have the social or environmental resources, nor understand, how to manage their disease symptoms, resulting in an increased disease burden and lower SRH.

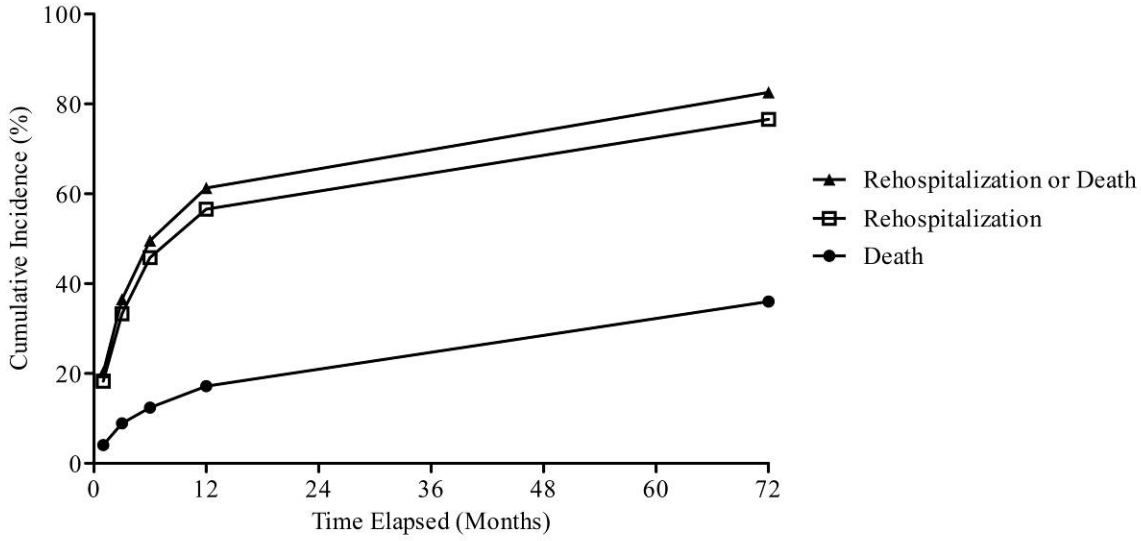
This dissertation brings to attention several areas for future research in cardiovascular disease epidemiology. The first is a need to better understand the relationship of socioeconomic status and the progression of heart failure in terms of its out-of-hospital management. The second is to explore the mechanisms underlying the relationship between poor socioeconomic status and increased mortality. Lastly, interventions can be tested to help understand how to improve SRH, and the resulting health outcomes, among aging adults.

VIII. APPENDICES

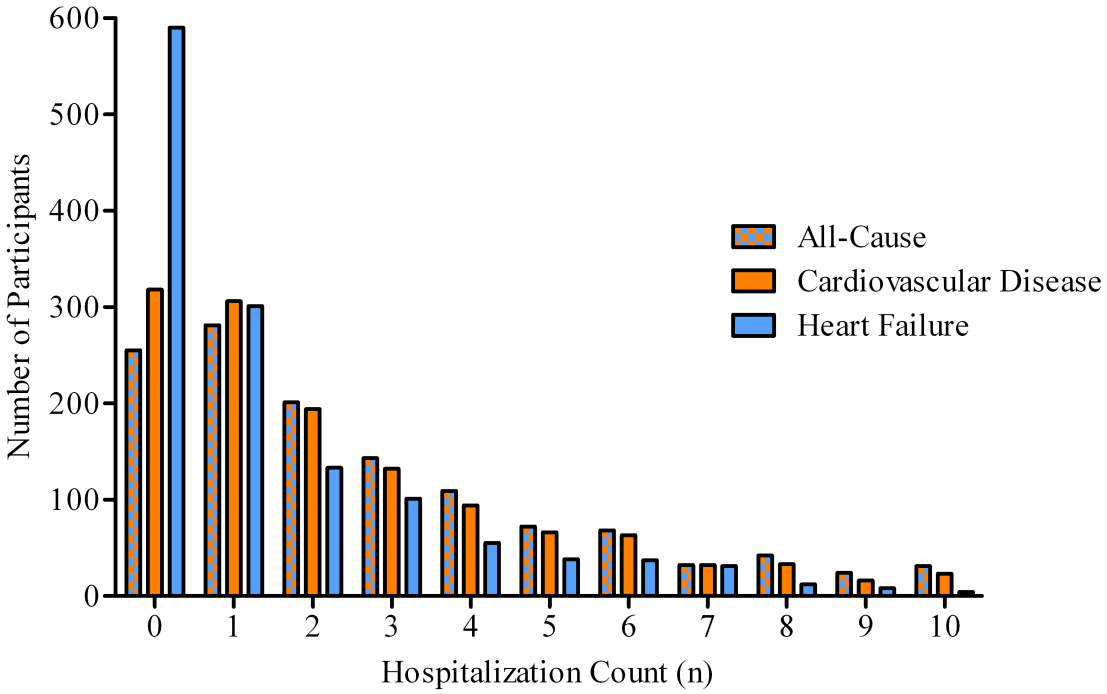
Appendix A. Prevalence of Charlson index components during the incident heart failure hospitalization, Overall and by nINC: The ARIC study, 1987-2004.

		Overall N=1,342		Median Household Income (nINC) Low N=553		Medium N=454		High N=335	
		N	%	N	%	N	%	N	%
Myocardial Infarction	Yes	170	12.7	57	10.3	74	16.3	39	11.6
	No	1,172	87.3	496	89.7	380	83.7	296	88.4
Peripheral Vascular Disease	Yes	105	7.8	38	6.9	36	7.9	31	9.3
	No	1,237	92.2	515	93.1	418	92.1	304	90.7
Cerebrovascular Disease	Yes	121	9.0	55	10.0	38	8.4	28	8.4
	No	1,221	91.0	498	90.0	416	91.6	307	91.6
Dementia	Yes	8	0.6	0	-	5	1.1	3	0.9
	No	1,334	99.4	553	100	449	98.9	332	99.1
Chronic Pulmonary Disease	Yes	368	27.4	124	22.4	153	33.7	91	27.2
	No	974	72.6	429	77.6	301	66.3	244	72.8
Rheumatologic Disease	Yes	33	2.5	11	2.0	13	2.9	9	2.7
	No	1,309	97.5	542	98.0	441	97.1	326	97.3
Mild Liver Disease	Yes	11	0.8	4	0.7	4	0.9	3	0.9
	No	1,331	99.2	549	99.3	450	99.1	332	99.1
Moderate or Severe Liver Disease	Yes	6	0.6	4	0.7	0	-	2	0.6
	No	1,336	99.4	549	99.3	454	100	333	99.4
Diabetes Mellitus	Yes	293	21.8	137	24.7	91	20.1	65	19.5
	No	1,049	78.2	416	75.3	363	79.9	270	80.5
Diabetes with Chronic Complications	Yes	55	4.1	20	3.6	16	3.5	19	5.7
	No	1,287	95.9	533	96.4	438	96.5	316	94.3
Hemiplegia or Paraplegia	Yes	20	1.5	9	1.6	11	2.4	0	-
	No	1,322	98.5	544	98.4	443	97.6	335	100
Renal Disease	Yes	37	2.8	22	4.0	8	1.8	7	2.1
	No	1,305	97.2	531	96.0	446	98.2	328	97.9
Charlson Index Score	0	474	35.3	187	33.8	167	36.8	120	35.8
	1	554	41.3	218	39.4	188	41.5	148	44.2
	2	215	16.0	97	17.6	69	15.2	49	14.6
	3	47	3.5	25	4.5	15	3.2	7	0.2
	4	39	2.9	17	3.0	11	2.5	11	3.2
	5	12	0.9	9	1.7	3	0.6	-	-
	6	1	0.1	-	-	1	0.2	-	-

Appendix B. Percent of participants who had died, were rehospitalized, or who had died or were rehospitalized following an incident hospitalized heart failure event: The ARIC study (1987-2004)



Appendix C. Distribution of rehospitalizations by type among participants with an incident hospitalized heart failure event, The ARIC study (1987-2004)



Appendix D. Rehospitalization status and characteristics of participants with incident hospitalized heart failure, overall and by nINC: The ARIC Study (1987-2004)

		Overall N=1,342		Median Household Income (nINC) Low N=553		Medium N=454		High N=335	
		N	%	N	%	N	%	N	%
Rehospitalized at least once		1087	81.0	458	82.8	369	81.3	260	77.6
30-day		246	18.3	81	14.6	112	24.7	53	15.8
90-day		447	33.3	174	31.5	186	41.0	87	26.0
6-month		614	45.8	240	43.4	236	52.0	138	41.2
1-year		759	56.6	306	55.3	279	61.5	174	51.9
5-year		1028	76.6	430	77.8	351	77.3	247	73.7
Mean follow-up, years		1.4		1.4		1.3		1.6	
Characteristics at Baseline									
Median Household Income (USD), mean		28,293		16,519		31,799		42,979	
Gender	Female	610	45.5	309	55.9	173	38.1	128	38.2
	Male	732	54.5	244	44.1	281	61.9	207	61.8
Race/Study Community	Black/Forsyth	45	3.4	26	4.7	17	3.7	2	0.6
	Black/Jackson	397	29.6	369	66.7	6	1.3	22	6.6
	White/Forsyth County	273	20.3	42	7.6	141	31.1	90	26.9
	White/Washington County	383	28.5	103	18.6	232	51.1	48	14.3
	White/Minneapolis	244	18.2	13	2.4	58	12.8	173	51.6
Hypertensive[a]		710	52.9	349	63.1	200	44.1	161	48.1
	Yes	621	46.3	200	36.2	251	55.3	170	50.8
	No	11	0.8	4	0.7	3	0.7	4	1.1
	Missing								
Body Mass Index (BMI)[b]	Obese	578	43.1	273	49.4	172	37.9	133	39.7
	Overweight	484	36.1	186	33.6	173	38.1	125	37.3
	Normal	278	20.7	93	16.8	109	24.0	76	22.7
	Missing	2	0.2	1	0.2	-	-	1	0.3
Current Drinker	Yes	621	46.3	168	30.4	237	52.2	216	64.5
	No	721	53.7	385	69.6	217	47.8	119	35.5
Current Smoker	Yes	473	35.3	204	36.9	161	35.5	108	32.2
	No	869	64.7	349	63.1	293	64.5	227	67.8
Educational Attainment, years	17-21	319	23.8	79	14.3	106	23.4	134	40.0
	12-16	498	37.1	169	30.6	190	41.9	139	41.5
	≤11	521	38.8	302	54.6	157	34.5	62	18.5
	Missing	4	0.3	3	0.5	1	0.2	-	-
Characteristics at Index Hospitalization									
Age, mean (SD)		67.0 (6.8)		66.0 (6.8)		67.9 (6.6)		67.5 (6.9)	
Charlson Comorbidity Index Score[2]	≥2	314	23.4	148	26.8	99	21.8	67	20.0
	<2	1,028	76.6	405	74.2	355	79.2	268	80.0
Medicaid Recipient[d]	Yes	135	10.1	111	20.1	15	3.3	9	2.7
	No	1,207	89.9	442	79.9	439	96.7	326	97.3

[a]Systolic blood pressure ≥140mmHg or diastolic blood pressure ≥90mmHg, or blood pressure medication in the last two weeks.
[b]Normal BMI: <25kg/m^2; overweight: 25-<29.5kg/m^2; and obese: ≥29.5kg/m^2
[2]Adapted for use with ICD-9-CM discharge codes
[d]As indicated in medical record

Appendix E. Odds ratios and 95% confidence intervals for rehospitalization among participants with an incident hospitalized heart failure event, The ARIC study (1987-2004)

	Charlson Index Score ≥2		Charlson Index Score <2	
	Model 1[a]	Model 2[b]	Model 1[a]	Model 2[b]
30-day				
nINC				
Low	2.07 (0.69, 6.15)	2.68 (0.80, 9.00)	1.33 (0.75, 2.33)	1.25 (0.70, 2.22)
Medium	1.28 (0.50, 3.30)	1.51 (0.57, 4.05)	2.04 (1.31, 3.18)	1.99 (1.25, 3.17)
High	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
Medicaid Recipient				
Yes	1.37 (0.54, 3.51)	1.27 (0.49, 3.29)	0.77 (0.37, 1.59)	0.69 (0.34, 1.42)
No	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
3-month				
nINC				
Low	2.30 (1.04, 5.08)	2.40 (1.05, 5.52)	1.64 (1.08, 2.50)	1.64 (1.04, 2.61)
Medium	1.98 (0.94, 4.15)	1.98 (0.92, 4.26)	2.08 (1.47, 2.95)	2.12 (1.44, 3.12)
High	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
Medicaid Recipient				
Yes	2.00 (0.89, 4.50)	1.90 (0.84, 4.32)	1.08 (0.70, 1.67)	1.03 (0.66, 1.62)
No	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
6-month				
nINC				
Low	1.64 (0.81, 3.35)	2.05 (0.96, 4.38)	1.19 (0.81, 1.75)	1.19 (0.79, 1.78)
Medium	1.84 (0.98, 3.48)	2.30 (1.23, 4.32)	1.55 (1.11, 2.15)	1.57 (1.11, 2.24)
High	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
Medicaid Recipient				
Yes	1.35 (0.62, 2.96)	1.18 (0.54, 2.57)	1.17 (0.77, 1.78)	1.16 (0.74, 1.81)
No	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
1-year				
nINC				
Low	1.87 (0.86, 4.10)	2.35 (1.05, 5.26)	1.25 (0.87, 1.78)	1.27 (0.87, 1.84)
Medium	2.01 (1.00, 4.04)	2.52 (1.24, 5.13)	1.54 (1.14, 2.08)	1.58 (1.14, 2.20)
High	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
Medicaid Recipient				
Yes	1.00 (0.47, 2.14)	0.89 (0.41, 1.94)	1.37 (0.93, 2.01)	1.37 (0.91, 2.07)
No	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)

	Charlson Index Score ≥2		Charlson Index Score <2	
	Model 1[a]	Model 2[b]	Model 1[a]	Model 2[b]
5-year				
nINC				
Low	1.03 (0.33, 3.21)	1.42 (0.44, 4.59)	1.23 (0.83, 1.81)	1.27 (0.85, 1.89)
Medium	1.18 (0.38, 3.61)	1.59 (0.48, 5.31)	1.25 (0.93, 1.68)	1.29 (0.95, 1.75)
High	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
Medicaid Recipient				
Yes	0.63 (0.28, 1.46)	0.58 (0.26, 1.32)	1.03 (0.65, 1.65)	0.99 (0.61, 1.58)
No	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)

[a]nINC and Medicaid status plus race/study community, gender and age at index event
[b]Model 1 plus hypertension, body mass index, current smoker, current drinker and educational attainment

Appendix F. Mortality status and characteristics of participants with incident hospitalized heart failure, overall and by nINC: The ARIC Study (1987-2004)

		Overall N=1,342		Median Household Income (nINC) Low N=553		Medium N=454		High N=335	
		N	%	N	%	N	%	N	%
Mortality Status Post-Index Hospitalization									
30-day		55	4.1	19	3.4	20	4.4	16	4.8
90-day		119	8.9	49	8.9	36	7.9	34	10.2
6-month		167	12.4	69	12.5	52	11.5	46	13.7
1-year		231	17.2	98	17.7	74	16.3	59	17.6
5-year		483	36.0	219	39.6	151	33.3	113	33.7
Mean follow-up, years		4.1		3.9		4.2		4.1	
Characteristics at Baseline									
Median Household Income (USD), mean		28,293		16,519		31,799		42,979	
Gender	Female	610	45.5	309	55.9	173	38.1	128	38.2
	Male	732	54.5	244	44.1	281	61.9	207	61.8
Race/Study Community	Black/Forsyth	45	3.4	26	4.7	17	3.7	2	0.6
	Black/Jackson	397	29.6	369	66.7	6	1.3	22	6.6
	White/Forsyth County	273	20.3	42	7.6	141	31.1	90	26.9
	White/Washington County	383	28.5	103	18.6	232	51.1	48	14.3
	White/Minneapolis	244	18.2	13	2.4	58	12.8	173	51.6
Hypertensive[a]	Yes	710	52.9	349	63.1	200	44.1	161	48.1
	No	621	46.3	200	36.2	251	55.3	170	50.8
	Missing	11	0.8	4	0.7	3	0.7	4	1.1
Body Mass Index (BMI)[b]		578	43.1	273	49.4	172	37.9	133	39.7
Obese		484	36.1	186	33.6	173	38.1	125	37.3
	Overweight	278	20.7	93	16.8	109	24.0	76	22.7
	Normal	2	0.2	1	0.2	-	-	1	0.3
	Missing								
Current Drinker	Yes	621	46.3	168	30.4	237	52.2	216	64.5
	No	721	53.7	385	69.6	217	47.8	119	35.5
Current Smoker	Yes	473	35.3	204	36.9	161	35.5	108	32.2
	No	869	64.7	349	63.1	293	64.5	227	67.8
Educational Attainment, years	17-21	319	23.8	79	14.3	106	23.4	134	40.0
	12-16	498	37.1	169	30.6	190	41.9	139	41.5
	≤11	521	38.8	302	54.6	157	34.5	62	18.5
	Missing	4	0.3	3	0.5	1	0.2	-	-
Characteristics at Index Hospitalization									
Age, mean (SD)		67.0 (6.8)		66.0 (6.8)		67.9 (6.6)		67.5 (6.9)	
Charlson Comorbidity Index Score[c]	≥2	314	23.4	148	26.8	99	21.8	67	20.0
	<2	1,028	76.6	405	74.2	355	79.2	268	80.0
Medicaid Recipient[d]	Yes	135	10.1	111	20.1	15	3.3	9	2.7
	No	1,207	89.9	442	79.9	439	96.7	326	97.3

[a]Systolic blood pressure ≥140mmHg or diastolic blood pressure ≥90mmHg, or blood pressure medication in the last two weeks.
[b]Normal BMI: <25kg/m^2; overweight: 25-<29.5kg/m^2; and obese: ≥29.5kg/m^2
[2]Adapted for use with ICD-9-CM discharge codes
[d]As indicated in medical record

Appendix G. Odds ratios and 95% confidence intervals for death among participants with an incident hospitalized heart failure event, The ARIC study (1987-2004)

	Charlson Index Score ≥2		Charlson Index Score <2	
	Model 1[a]	Model 2[b]	Model 1[a]	Model 2[b]
30-day				
nINC				
Low	Not estimable	Not estimable	0.66 (0.25, 1.78)	Not estimable
Medium	Not estimable	Not estimable	0.68 (0.32, 1.43)	Not estimable
High	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
Medicaid Recipient				
Yes	Not estimable	1.12 (0.89, 1.40)	1.82 (0.66, 5.05)	1.18 (1.04, 1.34)
No	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
3-month				
nINC				
Low	1.12 (0.33, 3.81)	1.15 (0.26, 5.17)	0.92 (0.52, 1.65)	0.89 (0.50, 1.58)
Medium	0.44 (0.12, 1.62)	0.45 (0.09, 2.27)	0.77 (0.46, 1.31)	0.72 (0.42, 1.23)
High	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
Medicaid Recipient				
Yes	0.91 (0.25, 3.25)	0.93 (0.25, 3.40)	1.33 (0.62, 2.85)	1.33 (0.58, 3.06)
No	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
6-month				
nINC				
Low	1.58 (0.53, 4.75)	1.91 (0.51, 7.23)	0.68 (0.38, 1.20)	0.63 (0.35, 1.16)
Medium	0.71 (0.24, 2.13)	0.79 (0.21, 2.90)	0.73 (0.45, 1.18)	0.67 (0.40, 1.12)
High	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
Medicaid Recipient				
Yes	1.19 (0.46, 3.03)	1.20 (0.47, 3.06)	1.21 (0.63, 2.30)	1.08 (0.53, 2.22)
No	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
1-year				
nINC				
Low	2.21 (0.79, 6.21)	2.44 (0.77, 7.79)	0.89 (0.56, 1.41)	0.87 (0.53, 1.43)
Medium	1.39 (0.56, 3.43)	1.45 (0.52, 4.05)	0.81 (0.55, 1.21)	0.77 (0.51, 1.18)
High	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
Medicaid Recipient				
Yes	1.20 (0.49, 2.96)	1.15 (0.47, 2.80)	0.86 (0.47, 1.59)	0.79 (0.41, 1.51)
No	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)

	Charlson Index Score ≥2		Charlson Index Score <2	
	Model 1[a]	Model 2[b]	Model 1[a]	Model 2[b]
5-year				
nINC				
Low	1.55 (0.74, 3.29)	1.65 (0.75, 3.63)	1.25 (0.88, 1.76)	1.17 (0.82, 1.68)
Medium	1.13 (0.60, 2.11)	1.13 (0.58, 2.18)	0.95 (0.67, 1.34)	0.93 (0.66, 1.32)
High	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
Medicaid Recipient				
Yes	0.90 (0.41, 1.99)	0.88 (0.39, 1.99)	0.83 (0.53, 1.30)	0.75 (0.46, 1.21)
No	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)

[a]nINC and Medicaid status plus race/study community, gender and age at index event
[b]Model 1 plus hypertension, body mass index, current smoker, current drinker and educational attainment

Appendix H. Rehospitalization or mortality status and characteristics of participants with incident hospitalized heart failure, overall and by nINC: The ARIC Study (1987-2004)

		Overall N=1,342		Median Household Income (nINC) Low N=553		Medium N=454		High N=335	
		N	%	N	%	N	%	N	%
Rehospitalized or Died		1171	87.3	491	88.8	394	86.8	286	85.4
30-day		273	20.3	92	16.6	119	26.2	62	18.5
90-day		490	36.5	191	34.5	198	43.6	101	30.2
6-month		666	49.6	262	47.4	250	55.1	154	46.0
1-year		822	61.3	332	60.0	295	65.0	195	58.2
5-year		1108	82.6	462	83.5	374	82.4	272	81.2
Mean follow-up, years		1.4		1.4		1.3		1.6	
Characteristics at Baseline									
Median Household Income (USD), mean		28,293		16,519		31,799		42,979	
Gender	Female	610	45.5	309	55.9	173	38.1	128	38.2
	Male	732	54.5	244	44.1	281	61.9	207	61.8
Race/Study Community	Black/Forsyth	45	3.4	26	4.7	17	3.7	2	0.6
	Black/Jackson	397	29.6	369	66.7	6	1.3	22	6.6
	White/Forsyth County	273	20.3	42	7.6	141	31.1	90	26.9
	White/Washington County	383	28.5	103	18.6	232	51.1	48	14.3
	White/Minneapolis	244	18.2	13	2.4	58	12.8	173	51.6
Hypertensive[a]		710	52.9	349	63.1	200	44.1	161	48.1
Yes		621	46.3	200	36.2	251	55.3	170	50.8
	No	11	0.8	4	0.7	3	0.7	4	1.1
	Missing								
Body Mass Index (BMI)[b]	Obese	578	43.1	273	49.4	172	37.9	133	39.7
	Overweight	484	36.1	186	33.6	173	38.1	125	37.3
	Normal	278	20.7	93	16.8	109	24.0	76	22.7
	Missing	2	0.2	1	0.2	-	-	1	0.3
Current Drinker	Yes	621	46.3	168	30.4	237	52.2	216	64.5
	No	721	53.7	385	69.6	217	47.8	119	35.5
Current Smoker	Yes	473	35.3	204	36.9	161	35.5	108	32.2
	No	869	64.7	349	63.1	293	64.5	227	67.8
Educational Attainment, years	17-21	319	23.8	79	14.3	106	23.4	134	40.0
	12-16	498	37.1	169	30.6	190	41.9	139	41.5
	≤11	521	38.8	302	54.6	157	34.5	62	18.5
	Missing	4	0.3	3	0.5	1	0.2	-	-
Characteristics at Index Hospitalization									
Age, mean (SD)		67.0 (6.8)		66.0 (6.8)		67.9 (6.6)		67.5 (6.9)	
Charlson Comorbidity Index Score[2]	≥2	314	23.4	148	26.8	99	21.8	67	20.0
	<2	1,028	76.6	405	74.2	355	79.2	268	80.0
Medicaid Recipient[d]	Yes	135	10.1	111	20.1	15	3.3	9	2.7
	No	1,207	89.9	442	79.9	439	96.7	326	97.3

[a]Systolic blood pressure ≥140mmHg or diastolic blood pressure ≥90mmHg, or blood pressure medication in the last two weeks.

[b]Normal BMI: <25kg/m^2; overweight: 25-<29.5kg/m^2; and obese: ≥29.5kg/m^2

[2]Adapted for use with ICD-9-CM discharge codes

[d]As indicated in medical record

Appendix I. Odds ratios and 95% confidence intervals for rehospitalization or death among participants with an incident hospitalized heart failure event, The ARIC study (1987-2004)

	Charlson Index Score ≥2		Charlson Index Score <2	
	Model 1	Model 2	Model 1	Model 2
30-day				
nINC				
Low	1.99 (0.69,5.70)	2.33 (0.73, 7.46)	1.19 (0.72, 1.98)	1.13 (0.68, 1.88)
Medium	1.01 (0.41, 2.48)	1.13 (0.44, 2.93)	1.79 (1.19, 2.69)	1.74 (1.14, 2.66)
High	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
Medicaid Recipient				
Yes	1.78 (0.75, 4.27)	1.67 (0.67, 4.12)	0.85 (0.42, 1.71)	0.77 (0.38, 1.57)
No	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
3-month				
nINC				
Low	2.18 (0.94, 5.08)	2.16 (0.89, 5.21)	1.41 (0.95, 2.10)	1.43 (0.94, 2.19)
Medium	1.39 (0.67, 2.89)	1.34 (0.63, 2.87)	1.89 (1.34, 2.66)	1.92 (1.32, 2.79)
High	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
Medicaid Recipient				
Yes	2.63 (1.19, 5.83)	2.43 (1.07, 5.53)	1.17 (0.75, 1.83)	1.15 (0.72, 1.84)
No	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
6-month				
nINC				
Low	1.78 (0.91, 3.47)	2.06 (1.01, 4.19)	Not estimable	1.09 (0.75, 1.59)
Medium	1.48 (0.85, 2.58)	1.75 (0.99, 3.08)	Not estimable	1.48 (1.07, 2.02)
High	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
Medicaid Recipient				
Yes	1.72 (0.76, 3.89)	1.47 (0.64, 3.37)	Not estimable	1.16 (0.72, 1.86)
No	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
1-year				
nINC				
Low	2.11 (0.94, 4.72)	2.46 (1.13, 5.34)	1.12 (0.79, 1.57)	1.17 (0.82, 1.68)
Medium	1.52 (0.80, 2.92)	1.85 (0.96, 3.57)	1.41 (1.06, 1.86)	1.45 (1.07, 1.96)
High	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
Medicaid Recipient				
Yes	1.25 (0.53, 2.95)	1.08 (0.44, 2.65)	1.41 (0.89, 2.22)	1.47 (0.91, 2.35)
No	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)

	Charlson Index Score ≥2		Charlson Index Score <2	
	Model 1	Model 2	Model 1	Model 2
5-year				
nINC				
Low	1.11 (0.23, 5.35)	1.47 (0.31, 6.96)	1.01 (0.68, 1.50)	1.08 (0.72, 1.62)
Medium	0.72 (0.18, 2.91)	0.97 (0.21, 4.39)	1.09 (0.81, 1.47)	1.14 (0.84, 1.55)
High	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
Medicaid Recipient				
Yes	0.71 (0.29, 1.75)	0.56 (0.23, 1.39)	1.19 (0.65, 2.15)	1.19 (0.65, 2.16)
No	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)

[a]nINC and Medicaid status plus race/study community, gender and age at index event
[b]Model 1 plus hypertension, body mass index, current smoker, current drinker and educational attainment

Appendix J. Rate ratios and 95% confidence intervals for rehospitalization or death among participants with an incident hospitalized heart failure event: Negative binomial regression, The ARIC study (1987-2004)

	Charlson Index Score ≥2		Charlson Index Score <2	
	Model 1[a]	Model 2[b]	Model 1[a]	Model 2[b]
All-cause Rehospitalization				
nINC				
Low	1.58 (0.98, 2.56)	1.84 (1.07, 3.18)	1.22 (0.94, 1.58)	1.16 (0.89, 1.52)
Medium	1.33 (0.89, 1.98)	1.50 (0.95, 2.37)	1.14 (0.94, 1.38)	1.12 (0.92, 1.37)
High	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
Medicaid Recipient				
Yes	0.80 (0.60, 1.07)	0.77 (0.58, 1.02)	1.47 (1.14, 1.90)	1.41 (1.09, 1.82)
No	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
CVD-related Rehospitalization				
nINC				
Low	1.70 (1.06, 2.71)	2.00 (1.17, 3.41)	1.16 (0.89, 1.50)	1.09 (0.83, 1.43)
Medium	1.31 (0.86, 2.01)	1.51 (0.92, 2.46)	1.15 (0.94, 1.41)	1.13 (0.91, 1.39)
High	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
Medicaid Recipient				
Yes	0.91 (0.67, 1.25)	0.88 (0.65, 1.19)	1.68 (1.30, 2.18)	1.61 (1.24, 2.09)
No	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
HF-related Rehospitalization				
nINC				
Low	1.58 (0.82, 3.06)	2.04 (0.93, 4.51)	1.16 (0.83, 1.63)	1.06 (0.74, 1.50)
Medium	1.47 (0.82, 2.66)	1.90 (0.97, 3.69)	1.15 (0.88, 1.51)	1.13 (0.85, 1.50)
High	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
Medicaid Recipient				
Yes	0.92 (0.59, 1.44)	0.84 (0.55, 1.29)	1.79 (1.28, 2.50)	1.65 (1.19, 2.27)
No	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)

[a]nINC and Medicaid status plus race/study community, gender and age at index event
[b]Model 1 plus hypertension, body mass index, current smoker, current drinker and educational attainment

Appendix K. Self-rated health among all participants, by contact year (CY) and nINC, The ARIC study (1987-2004)

		Self-Rated Health (SRH), Mean			
CY	N*	Overall	Low nINC	Medium nINC	High nINC
1	15,038	74.5	64.4	76.9	81.3
2	14,955	76.7	68.2	78.3	82.7
3	14,909	75.6	66.9	77.4	81.6
4	14,813	74.9	66.0	76.7	81.0
5	14,687	74.4	65.0	75.8	80.5
6	14,539	73.2	64.0	75.0	79.5
7	14,372	72.7	63.0	75.0	79.0
8	14,161	72.6	63.3	74.6	78.7
9	13,951	71.9	63.0	73.4	78.3
10	13,730	72.0	62.3	74.0	78.4
11	13,548	71.4	62.5	73.3	77.2
12	13,309	70.6	61.3	72.0	77.2
13	13,078	70.4	61.1	72.2	76.4
14	12,804	69.9	60.4	71.5	76.4
15	12,548	69.5	60.8	71.0	75.4
16	12,270	69.0	60.5	70.5	74.7
17	11,771	68.5	59.8	69.9	74.3

*Number of participants (of 15,038) who contributed non-missing SRH data for each CY

IX. REFERENCES

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