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Burden of Comorbidities and Functional and Cognitive Impairments in Elderly Patients at the Initial Diagnosis of Heart Failure and their Impact on Total Mortality. The Cardiovascular Health Study

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Abstract

Background—Comorbidities and functional and cognitive impairments are common in the elderly and often associated with greater mortality risk. However, the prevalence of these conditions and their associated mortality risk in elderly patients with incident heart failure (HF) is unknown.

Methods—We examined the prevalence of 9 comorbidities and 4 measures of functional and cognitive impairments in 558 participants from the Cardiovascular Health Study who developed incident HF between 1990 and 2002. Participants were followed prospectively until mid-2008 to determine their mortality risk.

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Results—Mean age of participants was 79.2 ± 6.3 years with 52% being men. Sixty percent of participants had ≥ 3 comorbidities, and only 2.5% had none. Twenty-two percent and 44% of participants had ≥ 1 activity of daily living (ADL) and ≥ 1 instrumental activity of daily living (IADL) impaired respectively. Seventeen percent of participants had cognitive impairment (modified mini-mental state exam (3MSE) score < 80, scores range between 0–100). During follow up, 504 participants died, with 1-year, 5-year, and 10-year mortality rates of 19%, 56%, and 83% respectively. In a multivariable-adjusted model, the following were significantly associated with greater total mortality risk (hazard ratio; 95% confidence interval): diabetes mellitus (1.64; 1.33–2.03); chronic kidney disease (1.32; 1.07–1.62 for moderate disease; 3.00; 1.82–4.95 for severe); cerebrovascular disease (1.53; 1.22–1.92); depression (1.44; 1.09–1.90); functional impairment (1.30; 1.04–1.63 for 1 IADL impaired; 1.49; 1.07–2.04 for ≥ 2 IADL impaired); and cognitive impairment (1.33; 1.02–1.73). Other comorbidities (hypertension, coronary heart disease, peripheral arterial disease, atrial fibrillation, and obstructive airway disease) and measures of functional impairments (ADLs and 15-foot walk time) were not associated with mortality.

Conclusion—Elderly patients with incident HF have a high burden of comorbidities and functional and cognitive impairments. Some of these conditions are associated with greater mortality risk.

Keywords

Heart Failure; Outcome; Comorbidities; Cognitive impairment; Functional impairment

INTRODUCTION

Heart failure (HF) afflicts 5.7 million individuals in the United States with 80% of those afflicted ≥ 65 years old (1, 2). Both incidence and prevalence of HF are high among the elderly (3). Elderly patients with HF have high mortality rates, with 1-year and 5-year mortality rates of 20% and 59% respectively among HF patients age 65–74 (1, 3, 4). Elderly patients frequently have multiple chronic diseases (comorbidities) and functional and cognitive impairments (5). These conditions may precede HF or develop during its course, and often negatively impact its outcome (6, 7). Several studies have evaluated the burden of comorbidities and functional and cognitive impairments in patients with prevalent HF, and the impact of these conditions on various HF outcomes (8–14). To our knowledge, however, the prevalence of these conditions in elderly patients prior to the diagnosis of HF and the impact they have on outcomes after HF has developed have not been assessed.

In this study, we examined the prevalence of key comorbid conditions and measures of functional and cognitive impairment in elderly patients at the time they are diagnosed with HF, and the impact of these conditions on total mortality, using a cohort of patients with incident HF in the NIH-funded, population-based Cardiovascular Health Study (CHS). These conditions were selected based on prior evidence suggestive of their association with worse outcome among patients with prevalent HF (8–14).

METHODS

Study cohort and study design

CHS is a population-based longitudinal study of cardiovascular disease in adults aged 65 years and older, funded by the National Heart, Lung, and Blood Institute (15). The study included 5,888 participants; of these, 5201 were recruited between 1989 and 1990 and 687 were recruited later between 1992 and 1993 in order to enhance minority representation in the cohort. Participants were recruited from 4 US counties (Forsyth county, NC; Sacramento county, CA; Washington county, MD; and Pittsburgh county, PA) (16). Participants were followed with annual clinic visits through 1998–1999 and with phone calls every 6 months, which are ongoing. During each clinic visit, participants had a full medical history, a physical examination, and a panel of tests that varied each year.

Our study cohort is an inception cohort of CHS participants with incident HF. All CHS participants with a new diagnosis of HF between 1990 and 2002 were included in the study cohort at the time of HF diagnosis. The burden of selected comorbidities and measures of physical and cognitive impairments was determined at baseline (the time of HF diagnosis) by carrying forward values from the most recent clinic visit preceding the diagnosis of HF. In order to minimize misclassification bias, carrying forward time was limited to a maximum of 3 years. Study cohort was followed prospectively until June 30, 2008, in order to determine the individual and collective impact of comorbidities and physical and cognitive impairments on total mortality. Since HF was one of the main outcomes of CHS, (others being coronary disease, angina, stroke, transient ischemic attack, claudication, and death) its diagnosis was adjudicated by a committee utilizing pre-specified and previously validated criteria. These criteria included having a new clinical diagnosis of HF made by a physician, and being actively on prescription medications for HF including both a diuretic and either a digitalis preparation or a vasodilator (17, 18). Participants who had an assessment of left ventricular ejection fraction (LVEF) following the diagnosis of HF were divided into 2 categories: heart failure with preserved ejection fraction (HFpEF) if LVEF was ≥ 45%; and heart failure with reduced ejection fraction (HFrEF) if LVEF was < 45%.

Baseline patient characteristics included age, sex, race, CHS center, smoking status, and body mass index (BMI). Measures of comorbidities included a general assessment of self-reported health status (good, fair, or poor) and the presence or absence of 9 specific comorbidities: hypertension (HTN), defined as having systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or actively treated with antihypertensive medications; diabetes mellitus (DM), defined as having fasting serum glucose ≥ 126 mg/dl, non-fasting serum glucose ≥ 200 mg/dl, or actively treated with oral hypoglycemic medications or insulin; chronic kidney disease (CKD), defined according to estimated glomerular filtration rate (eGFR) based on the Modification of Diet in Renal Disease Study (MDRD) equation(19) as moderate if: 60> eGFR ≥ 30 ml/min/1.73 m^2, or severe if : eGFR < 30 ml/min/1.73 m^2; Coronary heart disease (CHD), defined as having history of physician-diagnosed angina, myocardial infarction, or coronary revascularization; peripheral arterial disease (PAD), defined as having history of claudication or ankle-brachial index ≤ 0.8; atrial fibrillation (AF), defined as having rhythm consistent with AF on electrocardiogram during

clinic visit; cerebrovascular disease, defined as having adjudicated history of stroke or transient ischemic attack; obstructive airway disease, defined as having history of asthma, bronchitis, or emphysema; and depression, defined according to the CES-D scale as having patient-reported depressive symptoms for 3 or more days within the past week preceding clinic visit (20). Selected measures of functional impairment were impairments in activities of daily living (ADLs), including walking around the home, getting out of bed, eating, dressing, bathing, and using the toilet; impairment in instrumental activities of daily living (IADLs), including heavy housework, light housework, shopping, preparing meals, paying bills, and using the phone; and gait speed (meters per second) during clinic visit. Cognitive impairment was defined as having a modified mini-mental state examination (3MSE) score < 80 (21). The 3MSE score (range 0–100) has been shown to be a reliable screening tool for cognitive decline among CHS participants (22).

Statistical analysis

Patient characteristics and measures of comorbidities and functional and cognitive impairments were reported using percentages for categorical variables, and means and standard deviations (SD) for continuous variables. These were compared between men and women and between 3 different age groups (age: 66–75, 76–85, and > 85) using Fisher's test for categorical variables, and 2-sample t-test and analysis of variance for continuous variables. Normality was assessed and non-normally distributed continuous variables were log-transformed. Burden of comorbidities was measured as the total number of comorbidities, out of the 9 comorbidities selected. Correlations between the burden of comorbidities and self-reported health status and measures of functional and cognitive impairments were tested using Spearman correlation coefficients. To check for selection bias, sensitivity analysis was performed comparing patient characteristics of study cohort with those of participants with missing data.

Cox proportional hazards regression analysis was used to calculate 2 risk estimates (hazard ratio (HR)) of death associated with each patient characteristic and measure of comorbidities and physical and cognitive impairment among study participants. Estimate 1 was adjusted for patient characteristics including age, sex, race, BMI, smoking status, and CHS center, and was calculated using all available participants as well as based on participants with complete data. The "all available participant estimate" was done as a sensitivity analysis to assess for selection bias due to elimination of participants with missing values. Estimate 2 was adjusted for all baseline characteristics and was done only on the study cohort with complete data. A two-tailed alpha of 0.05 was used to determine significance of all statistical tests and parameter estimates. All HRs were reported with their 95% confidence intervals (CI). All analyses were performed using SAS 9.1 and SAS Enterprise Guide 4 (SAS Institue, Cary, NC, USA).

RESULTS

Prevalence of comorbidities and functional and cognitive impairments

During the period between 1990 and 2002, 1,193 CHS participants had a new diagnosis of HF of whom 558 participants had all baseline values of comorbidities and measures of

functional and cognitive impairments determined at the time of HF diagnosis and were included in the study cohort (table 1). Mean age of participants at the time of HF diagnosis was 79.2 ± 6.3 years, with 52% men and 87% whites. Among participants with known LVEF, HFPEF was more common in women than in men (54.9 versus 42.9%, P = 0.04) (table 1). The remaining 635 participants with missing data did not differ from the study cohort in respect to a wide range of patient characteristics available in both groups (age, sex, race, smoking status, and CHS center).

Burden of comorbidities was high among study participants. Sixty percent of participants had at least 3 of the 9 key comorbidities while only 2.5% had none. Among the selected comorbidities, HTN was by far the most common (82%) followed by CHD (60%). The prevalence of all selected comorbidities did not differ significantly between men and women except for CHD and PAD, which were more common in men than in women. Some comorbidities, including CHD, cerebrovascular disease, obstructive lung disease, and possibly DM, were more common in the younger age groups (66–75 and 76–85 years old) than in the oldest age group (older than 85 years) (table 1).

Functional impairment was common, with 10% of participants having ≥ 2 ADLs impaired and 17% having ≥ 2 IADLs impaired. Most functional impairment measures, including gait speed, were significantly worse in women and in the older age groups. Cognitive impairment (3MSE score < 80) was also common, affecting almost 1 of every 5 participants. Cognitive impairment did not differ significantly between men and women, but was significantly more common in the older age groups (table 1). Nearly 40% of participants reported having fair-to-poor health status. Burden of comorbidities significantly correlated with self-reported health status (Spearman correlation coefficient (ρ_S) = 0.29, $p < 0.0001$), and measures of functional impairment including number of ADLs impaired ($\rho_S = 0.15$, $p = 0.0003$), number of IADLs impaired ($\rho_S = 0.22$, $p < 0.0001$), and gait speed ($\rho_S = 0.13$, $p = 0.0027$). There was no correlation between burden of comorbidities and cognitive impairment.

Mortality risk associated with comorbidities and physical and cognitive impairments

During the follow-up period, lasting up to 18.3 years, 504 (90.3%) participants died. The median survival time was 4.3 years. Kaplan Meier estimates of 1-year, 5-year, and 10-year mortality were 19%, 56%, and 83% respectively. Table 2 reports minimally and fully adjusted HRs associated with each patient characteristic and measure of comorbidities and functional and cognitive impairments. The following were associated with significantly greater mortality risk: low BMI, DM, CKD, cerebrovascular disease, depression, impairment in IADLs, and cognitive impairment. The greater mortality risk associated with fair-to-poor self-reported health status, impairment in ADLs, lower gait speed, and PAD became non-significant in the fully adjusted model (table 2). There was a suggestion of greater mortality risk in participants with HFrEF as compared with those with HFpEF, which was not statistically significant. Other comorbidities including HTN, CHD, AF, and obstructive airway disease, and other measures of functional impairment were not associated with mortality (table 2).

DISCUSSION

To our knowledge, this is the first study to describe the population prevalence of key comorbidities and measures of functional and cognitive impairments in community dwelling older adults who subsequently develop HF, and to determine the individual and collective impact of these comorbidities and impairments on mortality during nearly two decades of follow-up. Our findings support three important conclusions. Elderly persons have high burden of comorbidities and functional and cognitive impairments even at the time of HF diagnosis. Some of these comorbidities and most measures of functional and cognitive impairments are associated with increased mortality. Other comorbidities, including established precursors of HF such as hypertension and coronary heart disease, do not impact mortality once HF diagnosis is established.

The present study confirms the high burden of comorbidities and functional and cognitive impairment reported in the elderly and in those with prevalent HF (8, 10–12, 23). The prevalence of certain comorbidities including DM, CHD, PAD, and obstructive airway disease decreased with age, likely due to survival bias. Other comorbidities and most measures of functional and cognitive impairments increased with age. There was modest, yet statistically significant correlation between the burden of comorbidities and the person's perception of health status and functional impairment.

The present study demonstrates that the high mortality among elderly persons with incident HF (19% at 1 year, 56% at 5 years, and 83% at 10 years) is in part attributable to the cumulative impact of key comorbidities and impairments at the time of HF diagnosis. Comorbidities associated with increased mortality include DM, CKD, cerebrovascular disease, and depression. These finding are consistent with what has been shown in other patient populations with prevalent HF (8, 24–26). Functional and cognitive impairments were also associated with increased mortality, supporting the growing awareness of the importance of these conditions in elderly patients with HF (26–30). Interestingly, contrary to established evidence in the elderly population, impairment in IADLs, and not in ADLs, was associated with increased mortality in our study cohort. One explanation is that individuals with impaired ADLs are more likely to depend on others for the management of their chronic conditions including HF, which may mitigate any adverse effect of on outcome. Conversely, individuals with impaired IADLs are more likely to continue to live independently, yet with various degrees of compromise to optimal management of their chronic conditions including HF, which may lead to worse outcome. The increased mortality risk seen in participants who had fair-to-poor SRHS was likely confounded by their associated comorbidities and physical and cognitive impairments, as this association became non-significant in the fully adjusted model (table 2).

The lack of association between two major precursors of HF, namely HTN and CHD, and mortality in our study participants with incident HF is an interesting finding. While HTN is a strong predictor of mortality in the general population, several studies have shown that elevated blood pressure does not predict mortality in persons with established HF (26, 31). CHD has been shown in other studies to be associated with increased mortality in both HFrEF and HFpEF (32, 33). However, prior studies have shown that ischemic etiology of

newly diagnosed HF was not associated with increased mortality (26, 34). These conflicting findings could be explained, at least in part, by the variability in defining CHD in different studies. In our study cohort, and others cited above, angina symptoms and prior myocardial infarction were considered diagnostic of CHD, while more contemporary studies relied mainly on angiography and prior revascularization in defining CHD. Similarly, the method used to define AF in our study cohort based on a single ECG during clinic visit, may have resulted in ascertainment bias responsible for the lack of association between AF and mortality in contrast to established evidence of such association (35, 36).

This study showed that high BMI, an established risk factor for HF(37), is associated with lower mortality risk, confirming the obesity paradox described in other populations with prevalent HF (38–42). Similar paradoxical relationships have been described with blood pressure, serum cholesterol, and serum albumin in their relationship with mortality in other patients populations with HF, end-stage renal disease, and terminal cancers (43, 44). It has been proposed that the presence of low BMI, low blood pressure, low cholesterol, and low albumin, in these patient populations may signify a greater problem of frailty and cachexia, both known to be associated with increased mortality (7).

Our findings have potential therapeutic implications. Despite the introduction of multiple drug classes with proven survival benefit in HFrEF, mortality rates in elderly HF patients have not declined over the past 2 decades (3). Furthermore most elderly patients have HFpEF, for which no pharmacological agents have yet shown mortality benefit. Our findings suggest that there are 3 key domains, namely comorbidities, functional impairment, and cognitive impairment, which help drive mortality in these elderly patients with HF. Therefore, targeting each of these three domains may provide the impetus for development of novel interventions with potential impact on survival and other outcome measures in elderly patients with HF (7). For instance, transitional care and multi-modality physical function interventions have recently been shown to improve outcomes in elderly patients with other disorders (45).

This study has several strengths related to the study population and study design. We used an inception cohort of very elderly persons with HF from a large prospective, population-based study with an exceptionally long follow-up. The inception cohort is less susceptible to survivor bias, and provides more accurate estimates of the effects of baseline comorbidities on prognosis of HF (46). HF was one of the primary outcomes of CHS; hence, its diagnosis was carefully ascertained and adjudicated by a committee utilizing pre-specified and validated criteria (17, 18). By including a wide range of clinically relevant comorbidities and measures of functional and cognitive impairments frequently seen in the elderly population, we were able to determine the collective impact of these conditions on the prognosis of elderly patients with incident HF.

Limitations inherent to the dataset and methods used may have impacted our findings. Selection bias due to excluding participants with missing values was found unlikely based on 2 types of sensitivity analyses. First, comparing participants excluded due to missing data with study cohort showed no significant differences between the 2 groups. Second, the more precise mortality risk estimates based on “all-available subject” fell within the 95% CI of the

estimate based on study participants with complete data for all predictor variables, except for depression (table 2). Misclassification bias may have resulted from imputing missing values by carrying them forward from prior clinic visits, a method that has been validated within the CHS population (47). Furthermore, since most of our imputed variables are chronic and persistent, any possible misclassification will potentially result in shrinkage of parameter estimates, driving any existing association toward the null (Type II error) (48). Misclassification bias might also have resulted from the method used to measure certain comorbidities (angina symptoms as a surrogate for CHD, random ECG during clinic visit as a surrogate for AF). The limited number of participants with known left ventricular ejection fraction precluded us from performing meaningful stratified analysis to explore any differential impact of comorbidities and impairments on HFrEF vs. HFpEF. The limited availability of certain comorbidity measures (such as hemoglobin, cholesterol, albumin, and surrogates for arthritis) restricted our ability to explore other clinically important comorbidities such as anemia, malnutrition, and arthritis, in the current study. We acknowledge that based on the significance level used (0.05) and the number of tests performed (19 in the fully adjusted model), at least 1 test might have yielded significant point estimate by chance. Lastly, we acknowledge that the diagnosis and management of HF has greatly evolved over the past 1–2 decades, which might have altered the complex relationship between HF and the associated comorbidities and impairments.

CONCLUSION

Elderly persons have a high burden of comorbidities and functional and cognitive impairments at the time they are diagnosed with HF. Some of these comorbidities and impairments are strongly associated with increased mortality risk, while other comorbidities, including known precursors of HF, are not associated with mortality. Given the high mortality rates observed in elderly patients with HF, research is needed to determine if therapeutic interventions and changes in the healthcare delivery designed to alter the course of the associated comorbidities and impairments would improve their survival.

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Abbreviations

HF	Heart failure
CHS	Cardiovascular health Study
BMI	Body mass index
LVEF	Left ventricular ejection fraction

HFpEF	Heart failure and preserved ejection fraction
HFrEF	Heart failure and reduced ejection fraction
HTN	Hypertension
DM	Diabetes Mellitus
CKD	Chronic kidney disease
CHD	Coronary heart disease
PAD	Peripheral arterial disease
AF	Atrial fibrillation
eGFR	Estimated glomerular filtration rate
ADLs	Activities of daily living
IADLs	Instrumental activities of daily living
3MSE	Modified mini-mental examination

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PERSPECTIVE

COMPETENCY IN MEDICAL KNOWLEDGE

Elderly persons have high burden of comorbidities and functional and cognitive impairments even at the time of heart failure (HF) diagnosis. Some of these comorbidities and most measures of functional and cognitive impairments are associated with increased mortality. Other comorbidities, including established precursors of HF such as hypertension and coronary heart disease, do not impact mortality once HF diagnosis is established.

TRANSLATIONAL OUTLOOK

Additional studies are needed to determine if therapeutic interventions and changes in the healthcare delivery designed to alter the course of the associated comorbidities and impairments would improve their survival of elderly patients with HF.

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Table 1

Study participants and prevalence of comorbidities and functional and cognitive impairments

Variable:	Total (N = 558)	By Sex			By age group			
		Women (n = 269)	Men (n = 289)	*P value*	66–75 yrs (n = 159)	76–85 yrs (n = 309)	> 85 yrs (n = 90)	*P value*
Age (years), mean ± SD	79.2 ± 6.3	79.0 ± 6.3	79.4 ± 6.3	0.46	71.8 ± 2.5	80.2 ± 2.9	89.0 ± 3.1	< 0.0001
Sex (men), %	51.8	-	-	-	49.7	52.1	54.4	0.76
Race (White), %	87.3	84.8	89.6	0.099	83.7	89.0	87.8	0.26
HFpEF, % *	48.3	54.9	42.9	0.04	51.6	47.3	43.8	0.7
BMI (kg/m²), mean ± SD	27.1 ± 4.8	27.5 ± 5.7	26.7 ± 3.8	0.059	28.6 ± 5.6	26.9 ± 4.3	25.2 ± 4.1	< 0.0001
Former smoker, %	45.9	33.1	57.8	< 0.0001	49.1	46.0	40.0	0.39
Current smoker, %	8.1	8.2	8.0	0.99	12.6	7.4	2.2	0.012
Fair-to-poor SRHS, %	39.1	39.4	38.8	0.93	37.1	39.5	41.1	0.81
Hypertension, %	82.1	84.8	79.6	0.12	77.4	84.8	81.1	0.13
Diabetes mellitus, %	28.5	25.7	31.1	0.16	35.2	26.7	22.2	0.06
Moderate CKD, %	28.5	29.0	28.0	0.85	25.2	28.8	33.3	0.39
Severe CKD, %	3.8	3.0	4.5	0.38	2.5	3.9	5.6	0.48
Coronary heart disease, %	59.3	50.9	67.1	< 0.0001	57.2	65.1	43.3	0.0009
Peripheral arterial disease, %	9.1	6.7	11.4	0.057	10.1	9.1	7.8	0.83
Atrial fibrillation, %	8.1	8.6	7.6	0.76	6.3	7.4	13.3	0.13
Cerebrovascular disease, %	20.4	19.3	21.5	0.60	15.1	24.3	16.7	0.043
Obstructive airway disease, %	19.7	19.0	20.4	0.67	22.0	22.0	7.8	0.0043
Depression, %	12.0	12.3	11.8	0.90	10.1	11.3	17.8	0.18
1 ADL impaired, %	12.5	14.9	10.4	0.13	8.8	14.6	12.2	0.21
≥ 2 ADL impaired, %	10.0	11.2	9.0	0.40	5.7	8.7	22.2	0.0003
1 IADL impaired, %	26.7	27.9	25.6	0.57	27.0	27.5	23.3	0.75
≥ 2 IADL impaired, %	17.0	22.3	12.1	0.0016	10.1	16.5	31.1	0.0002
Gait speed, meter/sec, mean ± SD	0.64 ± 0.36	0.56 ± 0.49	0.75 ± 0.20	< 0.0001	0.69 ± 0.37	0.68 ± 0.27	0.50 ± 0.20	< 0.0001
3MSE score ≤ 80. %	17.4	15.6	19.0	0.32	3.8	20.4	31.1	< 0.0001

* The percentage of HFpEF is based on only 294 participants with known left ventricular ejection fraction.

Abbreviations: SD: Standard Deviation; HFpEF: Heart Failure and preserved left ventricular Ejection Fraction; BMI: Body Mass Index; SRHS: Self-Reported Health Status; CKD: Chronic Kidney Disease; ADLs: Activities of Daily Living; IADLs: Instrumental Activities of Daily Living; 3MSE: Modified Mini-Mental State Examination.

Table 2

Risk of death associated with comorbidities and measures of functional and cognitive impairments

Variable:	Estimate 1*					Estimate 2†	
	All available Participants			Participants with Complete Data (N = 558)		Participants with Complete Data (N = 558)	
	N	HR (95% CI)	*P Value*	HR (95% CI)	*P Value*	HR (95% CI)	*P Value*
Body mass index (kg/m²)	1088	0.97 (0.96–0.99)	0.0003	0.98 (0.96–1.00)	0.067	0.97 (0.95–0.99)	0.0063
Fair-to-poor SRHS	1081	1.55 (1.36–1.77)	< 0.0001	1.59 (1.32–1.91)	< 0.0001	1.18 (0.96–1.47)	0.12
Hypertension	1088	1.08 (0.91–1.27)	0.40	1.16 (0.92–1.46)	0.21	1.06 (0.84–1.33)	0.65
Diabetes mellitus	1084	1.58 (1.36–1.82)	< 0.0001	1.75 (1.43–2.14)	< 0.0001	1.64 (1.33–2.03)	< 0.0001
Moderate CKD	689	1.37 (1.15–1.64)	0.0004	1.48 (1.21–1.80)	0.0001	1.32 (1.07–1.62)	0.0091
Severe and end-stage CKD	689	2.84 (1.80–4.47)	< 0.0001	3.04 (1.89–4.90)	< 0.0001	3.00 (1.82–4.95)	< 0.0001
Coronary heart disease	1088	0.96 (0.84–1.09)	0.49	1.01 (0.85–1.22)	0.88	0.99 (0.81–1.20)	0.88
Peripheral arterial disease	1088	1.51 (1.23–1.84)	< 0.0001	1.50 (1.10–2.03)	0.0098	1.19 (0.87–1.64)	0.29
Atrial fibrillation	1087	0.99 (0.80–1.23)	0.90	0.96 (0.69–1.32)	0.78	1.00 (0.72–1.40)	0.99
Cerebrovascular disease	1088	1.39 (1.20–1.62)	< 0.0001	1.67 (1.34–2.07)	< 0.0001	1.53 (1.22–1.92)	0.0003
Obstructive airway disease	839	1.16 (0.97–1.38)	0.11	1.11 (0.89–1.39)	0.34	1.10 (0.87–1.39)	0.43
Depression	1082	1.12 (0.93–1.36)	0.23	1.53 (1.16–2.00)	0.0022	1.44 (1.09–1.90)	0.011
1 ADL impaired	1084	0.96 (0.80–1.15)	0.63	1.19 (0.91–1.56)	0.21	0.96 (0.72–1.28)	0.96
2 or more ADLs impaired	1084	1.40 (1.17–1.68)	0.0003	1.52 (1.12–2.05)	0.0069	0.83 (0.56–1.22)	0.34
1 IADL impaired	1087	1.07 (0.93–1.23)	0.34	1.31 (1.06–1.61)	0.012	1.30 (1.04–1.63)	0.021
2 or more IADLs impaired	1087	1.64 (1.40–1.92)	< 0.0001	1.84 (1.42–2.37)	< 0.0001	1.49 (1.07–2.04)	0.017
Gait speed (meter/sec)	1059	1.02 (1.01–1.03)	< 0.0001	1.01 (1.00–1.02)	0.15	1.00 (0.98–1.02)	0.65
3MSE score < 80	1076	1.41 (1.19–1.67)	< 0.0001	1.29 (1.00–1.66)	0.05	1.33 (1.02–1.73)	0.033
HFrEF	577	1.18 (0.99–1.42)	0.066	1.20 (0.94–1.55)	0.15‡	1.18 (0.91–1.54)	0.22‡

*Estimate 1 is adjusted for patient specific characteristics including age, sex, race, smoking status, body mass index, and CHS center.

†Estimate 2 is adjusted for all variables in estimate 1 plus all measures of comorbidities and functional and cognitive impairments.

‡These estimates are based on a sample size of 294 participants with complete data who also have known left ventricular ejection fraction.

HFrEF: heart failure and reduced ejection fraction; SRHS: Self-reported health status; CKD: Chronic Kidney disease; ADLs: activities of daily living; IADLs: instrumental activities of daily living; 3MSE: modified mini-mental state examination; HFrEF: Heart Failure and reduced left ventricular Ejection Fraction.