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FUNCTIONAL CAPACITY AND RISK FOR HEART FAILURE
IN OLDER ADULTS

BY

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Degree to be awarded: M.P.H.
Executive MPH

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BY

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M.D., University of Patras, Greece, 1997

Thesis Committee Chair: Jose Binongo, PhD

An abstract of a Thesis submitted to the Faculty of the Rollins School of Public Health of Emory University in partial fulfillment of the requirements of the degree of Master of Public Health in the Executive MPH program 2014

Abstract

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Functional capacity is associated with several risk factors for heart failure (HF), including cardiovascular disease, elevated blood pressure, and diabetes; and also with mortality. Fit individuals have less risk for cardiovascular disease, hypertension, or diabetes, and lower mortality. Heart failure is an important public health problem with high socioeconomic burden and is significantly associated with age. Therefore, increasing physical activity at the population level might reduce the risk for HF and mortality. Several tests have been used to evaluate functional capacity. Walking tests are the most widely used, because of their simplicity and need of no special equipment or setting. The 6-minute walk test and its variants are widely used for prognostic reasons. However, because of the low ceiling and learning effect of 6-minute walk test, new walking tests have been introduced, especially for special populations. The long distance corridor walk (LDCW) test, introduced in the Health Aging and Body Composition (Health ABC) study, helps older individuals approach their maximum capacity, correlates strongly with oxygen consumption, and carries important prognostic information for mobility limitation and disability, cardiovascular disease, and all-cause mortality in older adults. There are limited data connecting functional capacity and incident HF in middle-aged individuals, and no data are available in older adults who have the highest rates for HF development. Therefore, evaluating the association of functional capacity with HF risk and mortality in older adults using data from well-designed cohort studies is a crucial step to inform the design of interventional studies. In this work, we examine the association between functional capacity, as assessed with the LDCW test, and risk for HF and mortality in older adults. For this purpose, we used 10-year follow-up data from the NIH-funded Health ABC Study, a population-based cohort of 3075 well-functioning, community-dwelling participants aged 70 to 79 years at inception (1997-1998) from Pittsburgh, PA, and Memphis, TN. We evaluated the association between exercise performance and cardiovascular responses recorded during the baseline (year 1) LDCW test and outcomes. Specifically for HF, we considered also the competing risk of mortality using appropriate statistical models. In multivariable models, we adjusted for risk factors previously linked to mortality and incident HF in this cohort along with other parameters linked with reduced functional capacity. Finally, we examined for modification effects of gender, race, and pre-existing cardiovascular disease on the association between functional capacity and 10-year outcomes (mortality and incident HF).

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Finally, I want to extend a special thank you to my husband, Andreas, for his unlimited support throughout my career -- and my twin newborns, because they were patient enough to allow me to complete my last EMPH classes before they decided they want out.

Functional Capacity and Risk for Heart Failure in Older Adults

Vasiliki V Georgiopoulou, MD

EMPH Candidate Fall 2014

1. Introduction

1.1 Project Objective

The purpose of this work is to investigate the association between functional capacity, as assessed with the long distance corridor walk test (LDCW), a two-stage, self-paced walking test similar to 6-min walk test (6MWT), and risk for incident heart failure (HF) and mortality at 10 years in older adults. For this purpose, we will use 10-year follow-up data from the NIH-funded Health, Aging, and Body Composition (Health ABC) Study. Briefly, the Health ABC Study is a population-based cohort of 3075 well-functioning, community-dwelling men and women aged 70 to 79 years at inception (1997-1998) from Pittsburgh, PA, and Memphis, TN. Specifically, we will construct unadjusted proportional hazards models and models adjusting for the Health ABC HF Score variables (Butler et al., 2008) plus additional variables linked to functional capacity and the outcomes of interest (incident HF and mortality); including age, gender, race, smoking status, body mass index, self-reported physical activity, prevalent cardiovascular disease (coronary artery disease, cerebrovascular disease, and peripheral vascular disease), depression, hypertension, diabetes, pulmonary disease, left ventricular hypertrophy (by ECG), electrocardiographic abnormalities, systolic and diastolic blood pressure, heart rate, and levels of creatinine, glucose, albumin, and cholesterol. We will also construct Kaplan-Meier curves for the LDCW completion categories (excluded, stopped, completed) and compare for mortality and HF risk using proportional hazards models. Also, we will use proportional hazards models to individually examine the association of each LDCW and cardiovascular response parameter with HF risk among completers of the test (LDCW). In secondary analyses, we will evaluate this association in gender and race groups and in relation to preexisting cardiovascular disease.

1.1 The Burden of Heart Failure in Older Adults as a Public Health Problem

1.1.1 The Public Health Problem of Heart Failure

Prevalence of HF is increasing significantly and because of these trends, HF is considered an “epidemic” and a public health priority in developed countries (Heidenreich et al., 2013; Teng, Finn, Hobbs, & Hung, 2010; Yeung et al., 2012). However, HF is a problem in developing countries as well and it is considered as a major non-communicable syndrome in these areas (Albert, 2008; Jiang & Ge, 2009). There are several etiologies for these increasing trends,

including (a) improved therapies and outcomes of acute cardiac conditions (for example, myocardial infarction), (b) increasing prevalence of lifestyle-related risk factors (for example, smoking, sedentary lifestyle, obesity), (c) advances in HF therapy (for example beta-blockers, angiotensin receptor blockers/angiotensin converting enzyme inhibitors/angiotensin antagonists, circulatory assist devices), and (d) aging of the population. On top of these, the lack of prevention strategies targeting HF enhances further the problem. Projections about the prevalence of HF in the United States report that the prevalence will increase by 23% in the next 20 years (Heidenreich et al., 2013).

Heart failure is a public health problem because of its significant socioeconomic burden. Its lifetime incidence is high; it is estimated at 20% to 30% for middle-aged persons (Bleumink et al., 2004; Huffman et al., 2013; D. M. Lloyd-Jones et al., 2002), and its prognosis remains poor, especially after a hospitalization for decompensation. Although there was a tremendous improvement with the advancements in HF therapies during the last decades, effective treatments to slow the progression of the disease after hospitalization for decompensation are lacking (Allen & O'Connor, 2007). In recent registries, the mortality 1 year after a hospitalization for HF ranges between 25% and 35% and seems to be consistent across healthcare systems (Chen, Normand, Wang, & Krumholz, 2011; Tavazzi et al., 2013; Teng et al., 2010; Yeung et al., 2012). Among outpatients, 5-year mortality ranges between 25 and 50% (Ammar et al., 2007; Bleumink et al., 2004; Hobbs et al., 2007; Roger et al., 2004). Heart failure adversely affects patients' quality of life also (Heo, Moser, Lennie, Zambroski, & Chung, 2007). However, beyond the direct impact on survival and patient quality of life, health care resource utilization and costs impose an escalating burden on health care systems and create major consideration. In 2012, total cost for HF was estimated to be $30.7 million and the direct medical costs was estimated to be $21 billion (Go et al., 2014). The total direct cost of HF in the United States is projected to increase from $21 billion in 2012 to $53 billion in 2030 (Heidenreich et al., 2013).

1.1.2 The Role of Aging in Heart Failure

Several factors have been shown to increase the incidence and prevalence of HF (Georgiopoulou, Kalogeropoulos, Sperling, & Butler, 2011); among them, age is a major determinant and, therefore, the aging of the population described worldwide is expected to have a considerable impact on the burden of HF. National Health and Nutrition Examination Survey

(NHANES) has provided important information on several diseases and health behaviors (Ford et al., 2010; Gu, Paulose-Ram, Dillon, & Burt, 2006; C. Li et al., 2011; J. Li, Thompson, Joseph, & Master, 2012; D. Lloyd-Jones et al., 2009; Ostchega, Dillon, Lindle, Carroll, & Hurley, 2004; Wang et al., 2010; Wright & Wang, 2011). Based on NHANES data from 2007-2010 (**Figure 1**), it is estimated that 5.1 million Americans aged ≥20 years have HF (Go et al., 2013) and the prevalence of the population is estimated at 2.4% for 2012 (Heidenreich et al., 2013). By year 2030, the prevalence of HF in US population is projected to reach 3.0% (Heidenreich et al., 2013).

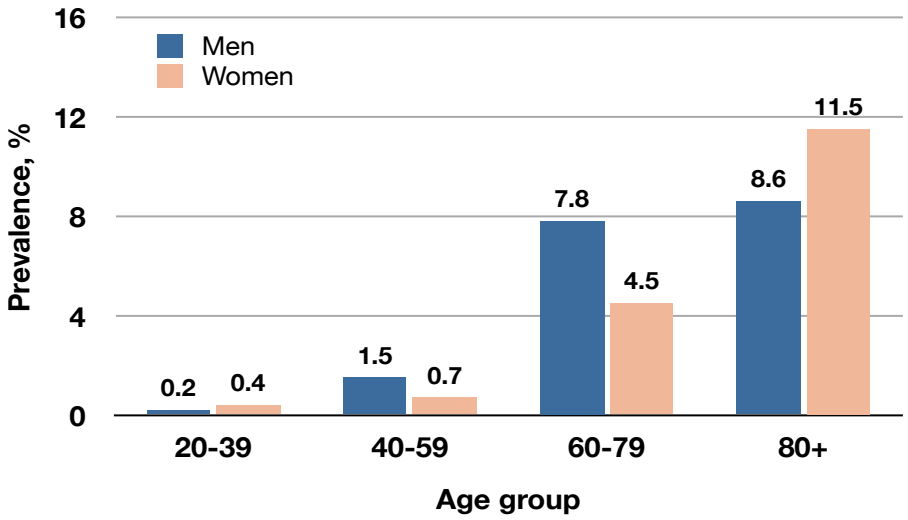


Figure 1. Prevalence of heart failure by gender and age in the United States (Source: National Health and Nutrition Examination Survey: 2007–2010).

Data recently published by the NHLBI-sponsored Cardiovascular Research Network report that approximately 12,000 new HF cases identified between 2005 and 2008 among adults enrolled in four participating healthcare plans in the United States (Gurwitz et al., 2013). Among these new HF cases 46% were women and 73% were over age 65 (Gurwitz et al., 2013). Notably, 52% of cases had preserved ejection fraction (EF), defined as equal or greater than 50%, and these patients were more likely to be women and over age 65 (Gurwitz et al., 2013). Other characteristics of the new HF cases were: (a) history of previous acute coronary syndrome or revascularization in <25%; (b) cerebrovascular disease in <20%; (c) atrial fibrillation or flutter in 30%; (d) hypertension in 75%; (e) diabetes mellitus in 19%; (f) concomitant chronic lung disease in 35%; (g) renal dysfunction (defined as estimated glomerular filtration rate <60 ml/min/1.73m^2) in <40%; (h) anemia (defined as hemoglobin <13g/L in men and <12g/L in

women) in <30%; and (i) depression and dementia in 16% and 7% of cases, respectively (Gurwitz et al., 2013). These data demonstrate a shift from a model where HF was mainly a consequence of coronary artery disease with male predominance towards a condition of older adults that equally affects both sexes and is accompanied by several comorbidities.

In the Atherosclerosis Risk in Communities (ARIC), a population-based study that recruited over 15,000 middle-aged participants (45 to 64 years old) between 1987 and 1989, the age-adjusted incidence of new HF hospitalizations was 5.7 per 1,000 person-years between 1987 and 2002 (Loehr, Rosamond, Chang, Folsom, & Chambless, 2008). Incidence rates were greater for blacks (men, 9.1; women, 8.1) than whites (6.0 and 3.4, respectively), **Figure 2A & 2B**; however, after adjustment for confounders this difference was lessened. Therefore, it is assumed that the higher prevalence of risk factors among blacks at cohort inception could in large part be responsible for the greater HF incidence observed in blacks (Loehr et al., 2008). In the Health, Aging, and Body Composition (Health ABC) Study, over 3,000 well-functioning participants aged 70 to 79 years were enrolled between 1997 and 1998. The incidence of HF over 7 years of follow-up was 15.8 per 1,000 person-years in men and 11.7 per 1,000 person-years in women (Kalogeropoulos et al., 2009). The higher incident rate in Health ABC population compared to that of ARIC reflect the effect of age on HF incidence. In Health ABC study, men and black participants were more likely to develop HF (**Figure 2C**). However, because the collection of new HF cases was based on hospitalization in both ARIC and Health ABC studies, the incidence of HF was likely underestimated. This seems to be the case, as in the Rotterdam Study (Netherlands), which included data from outpatient medical records and hospital discharge records, the incidence of HF after 7.1 years of follow up was considerably higher: 17.6 per 1,000 in men and 12.5 per 1,000 in women, despite the population was younger (age ≥55) (Bleumink et al., 2004).

Data from another study, where 360,000 adults enrolled in a large, managed-care organization in Georgia, United States, showed that the population incidence of HF, determined by administrative data from 2000 to 2005, was 3.9 cases per 1,000 patient-years (Goyal et al., 2010). Incidence was higher in men than in women (4.2 per 1,000 patient-years versus 3.7 per 1,000 patient-years); however, among the 4,000 new cases, >50% were women. Incidence increased considerably with age and men, who were younger than 75 years, demonstrated higher

rates. However, sex-based differences were no longer evident in the ≥75-year age group, **Figure 2D** (Goyal et al., 2010).

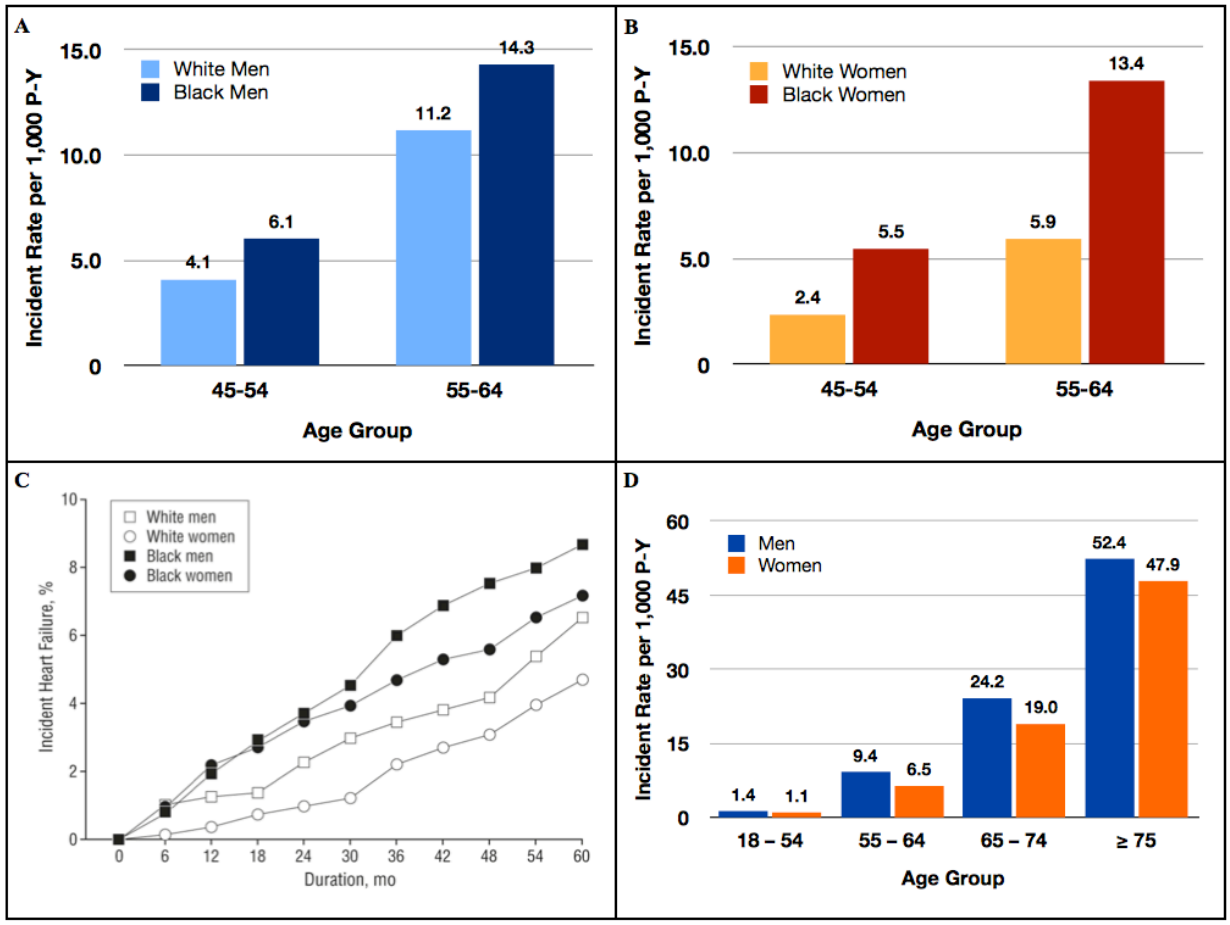


Figure 2. A & B: Heart failure incidence by sex, race, and age in the Atherosclerosis Risk in Communities (ARIC) cohort. (Data from Loehr et al, *Am J Cardiol* 2008; 101:1016-22). P-Y: person-years. C: Incident heart failure by sex and race in the Health, Aging, and Body Composition Study cohort. (Source: Kalogeropoulos et al, *Arch Intern Med* 2009; 169:708-15). D: Heart failure incidence among adults enrolled in a managed-care organization in Georgia, United States. (Data from Goyal A et al *Circ Heart Fail* 2010; 3:698-705, and personal communication with Dr. Abhinav Goyal).

1.2 Outcomes and Trends in Patients with Heart Failure

There was significant improvement in HF treatment over the past 20 years, which has led to notable improvement in HF outcomes. However, the absolute mortality and morbidity rates

still remain too high. For example, in a longitudinal analysis from Canada, adjusted 1-year mortality decreased from 17.7% in 1997 to 16.2% in 2007 for outpatients (Yeung et al., 2012). In another study from a single U.S. center, the unadjusted mortality decreased from 20.6% in 1993-98 to 17.8% in 2005-2010 in patients referred for advanced systolic HF (Loh et al., 2013). With the improvement in HF management most HF cases live longer and reach advanced stages of the disease; a fact that has led to increasing rates of death from progressive HF that in turn have offset the reductions in sudden death rates that were observed prior to new HF treatments. At the same time, the rates for heart transplants and mechanical circulatory support increased (Loh et al., 2013). In the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting (IMPROVE HF) registry, which included data from 167 outpatient cardiology practices in the United States, 2-year mortality was 22.1% among 11,600 patients with available vital status data (Fonarow et al., 2011).

Limited data exist on long-term outcomes among ambulatory HF patients. The majority of evidence suggests that, depending on underlying demographics and comorbid conditions, 50% to 75% of HF outpatients are alive by 5 years (Ammar et al., 2007; Hobbs et al., 2007; Roger et al., 2004).

1.3 Study Rationale: Exercise Capacity and Risk for Heart Failure

Exercise capacity is an important indicator of health considering that it reflects the function of several body systems. Exercise performance reflects a coordinated response of cardiovascular, pulmonary, neural, and muscles function. The function of the body systems, particularly the circulation and respiratory systems, is adequately tested only during exercise, because each system has reserve capacity exceeding that needed to sustain normal, asymptomatic body functioning at rest and during modest activity. Thus, impairment of this capacity reflects an impairment of body systems function. Aging is an important factor, among others, that predisposes to a decline of the function of various systems like muscular, (Nair, 2005), cardiovascular (Ferrari, Radaelli, & Centola, 2003), and respiratory (Janssens, Pache, & Nicod, 1999), and of the neuromuscular response times (Delbono, 2003) which in turn affects exercise capacity. Also, many disease processes, including psychological processes, such as depression or anxiety, (Wasserman, Hansen, Sue, Stringer, & Whipp, 2005) cause progressive loss of physiologic function of exercise-related systems by affecting the circulation or respiration

leading to reduced exercise capacity (Wasserman et al., 2005). These diseases are likely to manifest themselves initially by a reduction in cardiac or pulmonary reserve. By assessing the capability of individuals to perform exercise, the reserve capacity of each of the organ systems contributing to the exercise response is evaluated, at least in qualitative terms. During exercise, heart rate, arterial pressure, cardiac output, myocardial contractility, and rate and depth of respiration are increasing along with reversible shifts in the distribution of blood flow and blood composition. These changes are coordinated by the central nervous system (increased sympathetic stimulation and reciprocally decreased parasympathetic stimulation), which is responding to direct cortical input and to neural and humoral feedback from exercising muscles.

Considering the orchestrated coordination of all these systems and functions to produce the necessary exercise capacity, impaired exercise capacity in turn implies impaired health status. Impaired exercise capacity has been shown to be associated with increased risk for cardiovascular events (Peterson et al., 2008), hypertension (Barlow et al., 2006; Blair, Goodyear, Gibbons, & Cooper, 1984; Chase, Sui, Lee, & Blair, 2009; Williams, 2008), and diabetes mellitus (Sui et al., 2008; Wei et al., 1999; Williams, 2008). The prevalence of these conditions is higher in less-fit people. In addition, low functional capacity is associated with increased risk for mortality in both men and women, in whites and blacks, and in middle- and older age individuals (Blair et al., 1996; Blair et al., 1989; Gulati et al., 2003; Kokkinos et al., 2008; Mora et al., 2003; Myers et al., 2002; Sandvik et al., 1993; Sui, Laditka, Hardin, & Blair, 2007). In older adults, aged ≥60 years, a higher capacity to perform a maximal exercise test, is associated with reduction in all-cause mortality, independent of adiposity level (Sui, LaMonte, et al., 2007). For aged people (>70 years old), a poor performance on an extended walking test positively correlates with closer proximity to future health declines and mortality (Newman et al., 2006). For both healthy adults and those with cardiovascular disorders, low exercise capacity is a stronger predictor of decreased survival relative to other established risk factors, such as smoking, diabetes, or hypertension (Myers et al., 2002). In adults, reduced exercise capacity and diminished autonomic nervous system activity are predictive for future cardiovascular events and/or mortality (Myers et al., 2002; Tsuji et al., 1994; Zulfiqar, Jurivich, Gao, & Singer, 2010). Risk factors for cardiovascular disease develop early in life and tend to cluster in adulthood (Berenson et al., 1998). This could be prevented by physical activity, which is inversely related with clustering of cardiovascular disease risk factors in children and adolescents (Andersen et al.,

2006). In addition, alterations in cardiovascular health-related markers are already present early in life of inactive persons, like for example in healthy but inactive children and adolescents when compared to their active peers (Nagai & Moritani, 2004; Trigona et al., 2010). On the other hand, regular physical activity has been shown to favorably affect the cardiovascular system and improves cardiorespiratory fitness (Anderssen et al., 2007), endothelial function (Clarkson et al., 1999), and autonomic tone (Gutin et al., 2005; Nagai, Hamada, Kimura, & Moritani, 2004) in healthy individuals and in patients with pulmonary disease (Georgiopoulou et al., 2012) or HF (Dimopoulos et al., 2006).

Considering that the capacity for performing exercise depends on the ability of the heart to augment its output to the exercising muscles and the ability of these muscles to utilize oxygen from the delivered blood, the role of cardiac function is crucial for individuals' exercise performance. The increase in cardiac output may reach up to 4- to 6-fold in healthy subjects during exercise and especially during maximal exercise. This is accomplished by a 2- to 4-fold increase in heart rate and a 20% to 50% augmentation of stroke volume. The stroke volume increase is accomplished both by use of the Frank-Starling mechanism to maintain left ventricular end-diastolic volume and by more complete left ventricular emptying to reduce end-systolic volume. Both enhanced left ventricular contractility and peripheral vasodilation contribute to the more complete left ventricular emptying observed during exercise.

Cardiovascular disease has obvious limiting effects on the ability of the heart to increase cardiac output during exercise. Age, sex, and conditioning status also modify this response. Although with aging, maximum heart rate declines by approximately 1 beat per minute per year, age seems to have a relatively small effect on stroke volume. In the Baltimore Longitudinal Study of Aging (Fleg et al., 1995), volunteers were screened carefully by exercise and thallium scans to exclude silent coronary heart disease. Stroke volume during exhaustive upright cycle ergometry was unaffected by age (Fleg et al., 1995). However, aging affects the ability of the heart to reduce left ventricular end-systolic volume.

Reduced ability to perform aerobic exercise is a hallmark of HF. This reduction in aerobic capacity seems to be largely mediated by inadequate blood flow to skeletal muscle secondary to impaired cardiac output (Sullivan & Cobb, 1992; Wilson, Martin, Schwartz, & Ferraro, 1984). Patients with HF may achieve <50% of the maximal cardiac output attained by

healthy individuals at peak exercise. Stroke volume, which is already decreased at rest, rises only modestly up to a peak of 50 to 65 mL, compared with ≥100 mL in healthy subjects. The inability to increase cardiac output is related primarily to the minimal increase in stroke volume coupled with a lower maximal heart rate achieved at a lower workload (Sullivan & Cobb, 1992). In the dilated left ventricle and with reduced resting left ventricular systolic function, stroke volume typically increases only modestly during exercise because of a blunted ability to increase both left ventricular preload and ejection fraction (Sullivan & Cobb, 1992). The failure to increase left ventricular systolic emptying and thus augment left ventricular ejection fraction derives from a combination of impaired intrinsic contractility, reduced beta-adrenergic responsiveness, elevated systemic vascular resistance due to increased activity of the sympathetic and renin-angiotensin systems, and a blunted peripheral arterial vasodilator response to exercise.

Although there are data on the prognostic significance of functional capacity and cardiovascular response for the incidence of several conditions, there are limited data about functional capacity and cardiovascular response and risk for incident HF in middle-aged men (Farrell, Finley, Radford, & Haskell, 2013; Khan et al., 2014) and no data in the elderly, who have the higher rates of new onset HF (D. Lloyd-Jones et al., 2010).

In this direction, evaluating the effect of reduced functional capacity and cardiovascular responses on HF development is an important step to inform design of interventional trials.

1.4 Research Questions

Question #1:

a. Is functional capacity associated with risk for HF and mortality in older adults?

b. Is this association dependent on gender, race, and preexisting cardiovascular disease?

Question #2:

a. Is functional capacity change over time associated with risk for subsequent HF and mortality in older adults?

b. Is this association dependent of gender, race, and cardiovascular disease at baseline?

For (a) sub-questions, we will first examine whether there is an association. Then, using appropriate analytic methods, we will describe the association and perform appropriate transformations to meet assumptions for statistical inference.

Additional rationale for (b) sub-questions: reduced functional capacity predicts mortality stronger in women than in men (Gulati et al., 2003). Also, African-Americans appear to have a greater survival benefit from increased functional capacity (Al-Mallah et al., 2013); however, data are conflicted for gender-specific vulnerability (Al-Mallah et al., 2013; Kokkinos et al., 2008), so I think it is reasonable to explore any interaction with gender.

1.5 Project Assumptions and Contextual Considerations

The primary underlying assumption is that impaired functional capacity is associated with future mortality and HF in older adults. However, several factors may modify or confound this association (**Figure 3**).

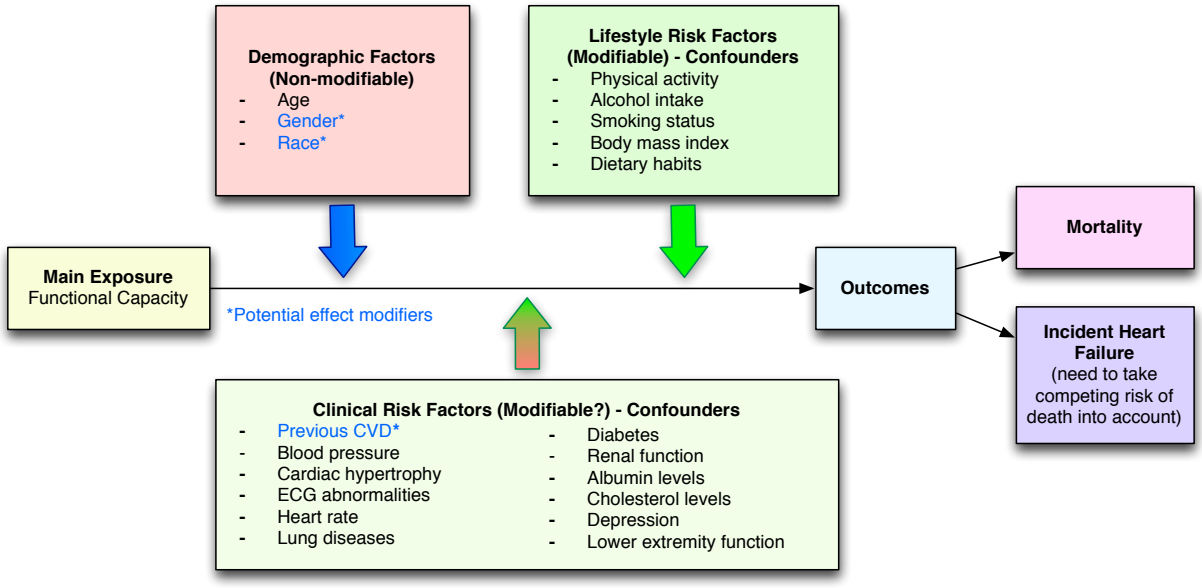


Figure 3. Conceptual model for the proposed project. Dietary sodium is considered as a modifiable risk factor in this context. CV: cardiovascular. ECG: electrocardiography

Based on previous clinical and mechanistic studies, we decided to test for modifying effects of race, gender, and preexisting cardiovascular disease. Although age might be an effect modifier in a different population, this is a homogeneous population of older adults. Therefore, we do not expect significant interactions with age. However, we will consider age as a

confounder and include it in the adjustment model. In case of no detection of interaction for gender, race, and baseline cardiovascular disease, in which case we will present separate analyses for these subgroups, we will consider these variables as potential confounders and include in the adjustment model.

We have classified the confounding factors into three categories: (1) demographic risk factors, generally considered as non-modifiable; (2) lifestyle-related risk factors for mortality, and HF generally considered as modifiable and (3) clinical risk factors. Previous work has shown that adequate control with therapy may attenuate the effects of some clinical risk factors, such as blood pressure, diabetes, etc.; however, the increased risk associated with these factors cannot be completely abolished. Also, some clinical risk factors are difficult to modify once present, e.g. previous cardiovascular disease or electrocardiographic abnormalities. Therefore, we have classified clinical risk factors separately.

The rationale for classification of confounders into categories based on amenability to modification is that, from a public health perspective, it might be important to know what fraction (if any) of the increased risk for these outcomes can be attributed to physical activity versus other modifiable factors. In other words, it might be useful to know what is the relative importance of modifiable factors for future events so that we can prioritize policies (Kalogeropoulos et al., 2009). Physical activity is considered a modifiable factor in this framework.

2 Literature Review

2.1 Functional Capacity and Mortality

The association between functional capacity and survival has been supported by several studies in healthy individuals (Blair et al., 1989; Ekelund et al., 1988; Myers et al., 2002) and persons with chronic conditions like cardiovascular disease (Davidson & DeBusk, 1980; Krone, Gillespie, Weld, Miller, & Moss, 1985; Myers et al., 2002; Vanhees, Fagard, Thijs, Staessen, & Amery, 1994), heart failure (Florea et al., 2000), chronic obstructive pulmonary disease, or diabetes mellitus (Kokkinos et al., 2009). Functional capacity also predicts mortality independent of age (Newman et al., 2006; Sandvik et al., 1993; Sui, Laditka, et al., 2007), race (Kokkinos et

al., 2008; Kokkinos et al., 2009), and gender (Blair et al., 1996; Gulati et al., 2003; Mora et al., 2003).

In a study analyzing the data from 3755 white men 30 to 69 years of age participating in the Lipid Research Clinics Prevalence survey that was conducted between 1972 and 1976, at 10 participating centers in the United States and Canada, exercise capacity was associated with higher risk of mortality (Ekelund et al., 1988). Specifically, among the participants, 3106 were healthy men and 649 had cardiovascular disease. There were 45 fatal cardiovascular events over an average follow-up period of 8.5 years. The cumulative mortality was much higher in the group of participants with the lowest level of fitness than in those who were more fit. The rate of death from cardiovascular disease was 8.5 times higher and that of death from coronary heart disease was 6.5 times higher. The relative risk of death from coronary heart disease for men in the group with cardiovascular disease, as compared with the healthy group, was 3.4, adjusting for other cardiovascular risk factors; their relative risk of death from cardiovascular disease was 2.8 (Ekelund et al., 1988). Also, in another study, physical fitness was a strong predictor of all-cause, cardiovascular, and cancer related mortality, after adjustment for known risk factors, in 13,344 individuals (10,224 men and 3,120 women) who received preventive medical examination (Blair et al., 1989). The relative risk for all-cause mortality was 3.44 in men and 4.65 in women (Blair et al., 1989). Similar findings were reported from another study of 6213 men referred for exercise testing for clinical reasons (Myers et al., 2002). The best predictor of increased risk of death among healthy subjects and those with cardiovascular disease was peak exercise capacity; hazard ratio was 0.84 (95% CI 0.79 to 0.89) and 0.91 (95% CI 0.88 to 0.94), respectively (Myers et al., 2002).

In 5,314 male older adults ≥65 years of age participating in the Veterans Exercise Testing Study, the mortality risk was 12% lower for each metabolic equivalent (MET) increase in exercise capacity. The hazard ratios across fitness categories were lower as the fitness was increasing ranged from 0.93 (95% CI, 0.83 to 1.04) for ≤5 METs to 0.39 (95% CI, 0.32 to 0.49) for those who achieved an exercise capacity >5 METs (Kokkinos et al., 2010). The adjusted relative risks across fitness categories were 32% to 63% lower in those who achieved an exercise capacity >5 METs in the group aged 65 to 70 years and 45% to 60% lower for those older than 70 years (Kokkinos et al., 2010). Higher capacity to perform better in a maximal exercise test is associated with lower risk for mortality in older adults also (Sui, LaMonte, et al., 2007). The

hazard ratios of mortality across incremental quintiles of fitness were 1.00, 0.53 (95% CI, 0.40 to 0.70); 0.51 (95% CI, 039 to 0.68); 0.52 (95% CI, 040 to 0.69); 0.53 (95% CI, 040 to 0.71); 0.54 (0.41 to 0.72) independent of adiposity status (Sui, LaMonte, et al., 2007). Notably, increased exercise capacity is associated with increased survival (Faselis et al., 2014). For every MET increase in exercise capacity, risk of mortality was 11% lower (hazard ratio, 0.89; 95% CI, 0.86 to 0.93). Compared with men who achieved ≤4.0 METs on the exercise test, risk of mortality was lower by 18% for the low-fit (hazard ratio, 0.82; 95% CI, 0.70 to 0.95), by 36% for the moderate-fit (hazard ratio, 0.64; 95% CI, 0.52 to 0.78), and by 48% for the high-fit (hazard ratio, 0.52; 95% CI, 0.39 to 0.69) (Faselis et al., 2014). Exercise capacity has been shown to be a strong risk factor for mortality in African-Americans also; however, it has been reported that the association between exercise capacity and mortality was stronger in whites than in African-Americans. A 19% lower risk for Caucasians and 14% for African Americans has been reported for each 1-MET increase in exercise capacity. The risk was 43% lower (0.57 [95% CI, 0.44 – 0.73]) for moderate-fit and 67% lower (0.33 [95% CI, 0.22– 0.48]) for high-fit Caucasians, whereas the comparable reductions in African Americans were 34% (0.66 [95% CI, 0.55– 0.80]) and 46% (0.54 [95% CI, 0.39 – 0.73]), respectively (Kokkinos et al., 2009). In a study with asymptomatic women higher exercise capacity levels were associated with lower risk for mortality; 17% decreased risk for every 1-MET increase, after adjustment for the Framingham Risk Score (Gulati et al., 2003). Similar findings have been reported in patients with chronic obstructive disease (Pinto-Plata, Cote, Cabral, Taylor, & Celli, 2004) or diabetes (Nylen, Kokkinos, Myers, & Faselis, 2010). It has been reported that functional capacity and its decline over time as measured by the 6MWD test was a significant predictor of survival in patients with respiratory disease, with a risk ratio of death of 0.82 (95% CI, 0.72 to 0.94) per 50 m increase in the decline of distance walked during the 6MWD test (Pinto-Plata et al., 2004). In 2,867 middle-aged and older men with diabetes mellitus, exercise capacity was associated with risk for mortality in both age groups (Nylen et al., 2010). Specifically, for each 1-MET increase in exercise capacity, mortality was 18% lower for the entire cohort (HR, 0.82; 95% CI, 0.79 to 0.86), 23% lower in middle-aged men (HR, 0.77; 95% CI, 0.73 to 0.82), and 16% lower for older men (HR, 0.84; 95% CI, 0.8 to 0.89) (Nylen et al., 2010). When fitness categories were considered, the mortality risk was 30% to 80% lower for those who achieved more than 4 METs in both age groups (Nylen et al., 2010).

2.2 Functional Capacity and Heart Failure

A wealth of data supports the association between functional capacity and incidence of cardiovascular disease or other conditions (Newman et al., 2006; Seyoum, Estacio, Berhanu, & Schrier, 2006; Williams, 2008). Other traditional risk factors for HF except for cardiovascular disease, like hypertension, and diabetes are also associated with impaired exercise capacity (Williams, 2008). Considering the association of HF risk factors with exercise capacity and the importance of cardiac function on exercise performance, impaired functional capacity could be a precursor of HF development. It has been reported that exercise training enhances cardiac function, even in older adults (Seals et al., 1994; Spina, Turner, & Ehsani, 1997), underscoring that impaired exercise capacity could be responsible for reduced cardiac function or indicate an early symptom of HF development. However, to date limited data are available about functional capacity and incident HF (Farrell et al., 2013; Khan et al., 2014). These data refer to middle-aged men. No data on functional capacity and older adults are available. A direct association between functional capacity and risk for HF in older adults has yet to be demonstrated. Because of the higher incidence rates of HF in older adults, this association is especially important for this age population.

2.3 Summary

Heart failure is an important public health problem with high socioeconomic burden (Go et al., 2014). Whether exercise capacity is associated with incident HF in all age groups is unknown. Aging is linked with impaired exercise capacity and is associated with higher HF incidence rates. Considering that impaired functional capacity has been shown to be associated with HF in middle-aged adults (Farrell et al., 2013; Khan et al., 2014) and that it is a predictor of mortality, cardiovascular disease development, diabetes, and hypertension – all risk factors for HF development – functional capacity could predict development of HF in older adults as well. Also, exercise training enhances cardiac function, even in older adults, which underlines that low levels of exercise capacity might be associated with impaired cardiac function. Towards this direction, evaluating the association of functional capacity with mortality and HF development in older adults using data from well-designed cohort study will provide information about possible interventions to prevent development of HF and reduce the public socioeconomic burden. Our

purpose is therefore to investigate the association between functional capacity, as assessed by the LDCW test, and risk for (1) all-cause mortality and (2) incident HF in older adults.

3 Data Collection, Analysis and Results

3.1 Study Design Overview

Data from a prospective cohort study are used for the current study. The prospective cohort design is considered a strong design. Actually the evidence originated from this type of studies are considered second only to that provided from randomized controlled trials. A well-designed cohort study can provide powerful results. However, there are several weaknesses associated with cohort studies as well. In this section, we briefly summarize strengths and weaknesses of the prospective cohort design and discuss the application of these issues in the Health ABC Study, which was used for this analysis.

3.1.1 Basic Design of Cohort Studies

In a cohort study, an outcome or disease-free study population is first identified by the exposure or event of interest and followed over time until the disease (incidence) or outcome of interest occurs. The incidence of disease in the exposed group is compared with the incidence of disease in the unexposed group. Because exposure is identified before the outcome, cohort studies have a temporal framework to assess causality and thus have the potential to provide the strongest scientific evidence. Exposure (e.g. level of functional capacity) is measured at baseline and/or assessed at intervals during follow-up. Data about the exposure may be obtained from several sources including medical records, standardized questionnaires, interviews, laboratory or other tests, or physical examination. Data related to outcomes may be obtained from various sources as well, including routine surveillance, death certificates, medical records, or directly from the participant. The follow-up period for a cohort study is a significant challenge and requires time and a lot of resources (financial and non-financial) to ensure adequate follow-up period and update measures of exposures and confounders, in addition to monitoring outcomes.

The probability of having the outcome of interest will be affected by the selection of subjects into a cohort study. The *'healthy entrant effect'* occurs because of the necessity of an almost *disease-free* or *healthy* status on entry to the study. In Health ABC study older individuals should be relatively healthy and able to walk at least a quarter of a mile or climb one flight of stairs without resting in order to be enrolled in the study. Therefore, initially, subjects are seen to

have lower levels of disease than might be true of the population in general, with an acceleration of disease rate over time. Follow-up of subjects is carried out to monitor changes in health status over time. It is essential to have a mechanism in place that achieves the lowest possible dropout rate from the study.

3.1.2 Potential Sources of Bias in Cohort Studies

A major source of potential bias in cohort studies is loss to follow-up. Loss to follow-up will increase with the length of study. Cohort members may die, migrate, or refuse to continue to participate. In addition, losses to follow-up may be related to the exposure, outcome or both. For example, individuals who develop the outcome may be less likely to continue to participate in the study. Loss to follow-up associated with the exposure and/or the outcome introduces bias in the measures of effect of exposure. In the Health ABC Study, there was specific inclusion criterion to reduce losses to follow-up. Specifically, only participants planning to live in the designated geographic areas for ≥3 years were included, whereas surveillance was very rigorous (telephone contact every 6 months and annual physical visit). As a result, follow up status was complete after 10 years for >99% of participants and vital status was obtained and available practically for every patient. In addition to the number of dropouts, any systematic differences related to the outcome or exposure to risk factors, between those who drop out and those who stay in the study, could potentially bias the study. Sensitivity analysis is thus essential: a comparison of risk factors is made between individuals who remain in the study and those who have dropped out. If loss to follow-up is ignored, the validity of study conclusions may be called into question.

Another source of potential bias in cohort studies arises from the degree of accuracy with which subjects have been classified with respect to their exposure or disease status at baseline. Differential misclassification can lead to an over- or under-estimate of the effect of the exposure on the outcome. We discuss these issues in the "measurement of main exposure of interest" and "baseline disease status classification" sections below.

Selection bias may be introduced not only when the completeness of follow-up or case ascertainment differs between exposure categories, but also when selection of participants is not representative of the intended population. In the Health ABC Study, selection bias was present by design, because the study enrolled only older adults reporting no difficulty walking a quarter

of a mile, climbing one flight of stairs without resting, or performing basic activities of daily living. Persons who required an assistive device, such as a cane or walker, were excluded. The findings of the study should therefore be interpreted in the context of well-functioning older adults and cannot be extrapolated to the general population of older adults.

3.1.3 Strengths and Weaknesses of Cohort Studies

We summarize here briefly the strengths and weaknesses of the cohort study design in the context of the research question and the current cohort study:

Strengths:

- Multiple outcomes can be measured.
- The change in exposure and outcome over time can be measured.
- Multiple exposures can be investigated (although not directly applicable to the research question, it allows to account for potential important exposure covariates).
- There is a natural course: measurement of cause (exposure) is performed before the effect (onset of disease).
- The temporal dimension (exposure is seen to occur before outcome) gives some indication of causality.
- Incidence and prevalence of the desired outcomes can be measured.

Weaknesses:

- Confounding is not rare in cohort designs.
- Insight into relevant determinants is necessary.
- There is no insight into selection through preceding exposure of determinant.
- Participants may move between exposure categories (regression dilution).
- Changes in etiology of disease over time may be hard to disentangle from changes observed as age increases.
- Knowledge of exposure status may bias classification of the outcome.
- Being in the study may have altered participant's behavior.
- Classification of individuals (exposure or outcome status) might have been affected by differences in diagnostic procedures.

3.2 Measurement of Main Exposure of Interest

Functional capacity was assessed using the Long Distance Corridor Walk (LDCW) test, which was performed at baseline (year 1) and during the follow-up visit of year 4 of the Health ABC Study. This test was performed in a course of 20 m, which was marked by traffic cones at both ends. It is a two-part, self-paced walking test. The first part consisted of a 2-minute warm-up walk in which participants were instructed to "cover as much ground as possible," which served as a warm-up and provided data for those unable to walk for a longer period. The second part consisted of a 400-m walk "done as quickly as possible." The course was 20 m long and marked by cones at each end. For the 2-minute walk, subjects were instructed to walk down the corridor, around the traffic cone, and back, in a continuous fashion, covering as much ground as they could in 2 minutes. Standard encouragement was given each lap and subjects were also told, ''You have 30 seconds to go,'' ''10 seconds to go,'' and ''Stop. Stay where you are.'' Ending heart rate, Borg perceived exertion rating (Borg & Linderholm, 1967), time, and a manual count of full and partial steps taken for the first 20 m and laps and meters completed were recorded. Within 30 seconds of completion, subjects were brought back to the start for the 400-m walk and instructed to complete 10 laps ''as quickly as possible.'' At the end of each lap, standard encouragement was given, as well as laps remaining (e.g., ''4 down, 6 to go''). Seconds to complete 400 m, ending heart rate and systolic blood pressure, and Borg perceived exertion rating (Borg & Linderholm, 1967) were recorded. Before testing, a portable heart rate monitor was placed on the subject, and pretest heart rate was recorded (Polar Pacer, Model 61190, Polar Electro, Oy, Finland). Heart rate was also monitored continuously by the Polar Pacer. For safety purposes, the examiner was instructed to stop subjects during either walk if their heart rate exceeded 170 beats per minute or they reported chest or leg pain, dyspnea, dizziness, feeling faint, or other significant symptoms.

Tests of varying complexity have been used to evaluate exercise capacity, ranging from distance to be covered in predefined time (e.g. the 6-min walk test) to simultaneous acquisition of several cardiovascular, ventilatory, and gas exchange variables (cardiopulmonary exercise testing). The latter provide pathophysiologic insights that are important for diagnosis (Sue & Wasserman, 1991), risk assessment (Sue & Wasserman, 1991), and decision-making (Sue & Wasserman, 1991); however, these tests cannot be widely performed due to the requirement of

special equipment and expertise. Therefore, walking tests have been introduced, allowing for wider implementation of functional capacity testing and evaluation of patients who are unable to complete complex protocols as a result of underlying comorbidities or age. The 6-min walk test (6MWT) is easy to perform, correlates strongly with oxygen consumption (Cahalin, Pappagianopoulos, Prevost, Wain, & Ginns, 1995; Peeters & Mets, 1996), and has prognostic value in chronic conditions (Bittner et al., 1993; Casanova et al., 2008). However, 6-min walk test and its variants have some disadvantages, including a low test ceiling (Frost et al., 2005), subject motivation (Clark, Poole-Wilson, & Coats, 1994; Guyatt et al., 1984), and learning effects (Wu, Sanderson, & Bittner, 2003). To overcome these drawbacks, the LDCW, similar to 6MWT, was introduced in the Health ABC Study (Klepin et al., 2010; Simonsick, Montgomery, Newman, Bauer, & Harris, 2001; Simonsick, Newman, et al., 2001; Simonsick et al., 2008). The LDCW helps older individuals approach their maximum capacity (Simonsick, Montgomery, et al., 2001), correlates strongly with oxygen consumption (Simonsick, Fan, & Fleg, 2006) and carries important prognostic information for mobility limitation and disability, cardiovascular disease, and all-cause mortality (Newman et al., 2006). However, the value of LDCW for HF risk prediction, and importantly, for refining HF risk assessment over simple clinical risk factors, has not been reported yet.

3.3 Baseline Classification of Disease Status

Baseline data for the cohort participants (inception period) were collected from April 1997 to June 1998. Cardiovascular disease status at baseline, including prevalent cardiovascular disease and HF, was based on self-reported history, use of selected drugs, and the *International Classification of Diseases, Ninth Revision, Clinical Modification* codes as reported by Medicare and Medicaid Services from 1995 through 1998. Prevalent cardiovascular disease was defined as (1) prevalent coronary heart disease (history of myocardial infarction, angina treated with medications, or coronary revascularization); (2) prevalent cerebrovascular disease (history of stroke, transient ischemic attack, or carotid endarterectomy); or (3) prevalent peripheral vascular disease (history of intermittent claudication or vascular bypass or angioplasty). Prevalent HF was defined as physician diagnosis of HF followed by treatment for HF (i.e., a current prescription for a diuretic agent and either digitalis or a vasodilator) (Kalogeropoulos et al., 2009).

3.4 Surveillance Methods of Event

In the Health ABC Study, surveillance was conducted every 6 months. Two methods were used: (i) in-person examination; (ii) telephone interview. Participants were asked to report any hospitalizations and were also asked direct questions regarding cardiovascular disease and HF events during the planned telephone interviews or in-person examinations. Medical records for overnight hospitalizations were reviewed and adjudicated at each site by local adjudicators. Algorithms similar of those of the Cardiovascular Health Study were used (Fried et al., 1991), by a group of clinicians who verified diagnoses and cause of death based on interview, review of all hospital records, and death certificates. It is important to emphasize that physicians, subsequently adjudicated all events captured through patient self-report, using copies of hospital records and other source documents. Therefore, the Health ABC Study is not relying on self-reported elements for adjudication; self-report is used only for event surveillance.

4 Data Collection, Analysis, and Results:

4.1 Population

The participants for the Health ABC study should meet specific criteria in order to be considered as eligible candidates. Specifically, the eligibility criteria are:

i. Age 70 to 79 at inception
ii. No difficulty performing activities of daily living
iii. Walking one-quarter of a mile, or climbing 10 steps without resting
iv. No reported need of assistive devices (e.g., cane, walker)
v. No active treatment for cancer in the prior 3 years
vi. No life-threatening illness
vii. No participation in a clinical or lifestyle intervention trial
viii. No plans to leave the area for 3 years

4.2 Description of the Data Sources

The Health ABC study was designed to assess the relationship between body composition, long-term conditions, and incident mobility limitation in an initially well-

functioning older adult cohort. This study aims to characterize the extent of change in body composition in older men and women, identify clinical conditions accelerating these changes, and examine the health impact of these changes on strength, endurance, disability, and weight-related diseases of old age. From March 1997 to April 1998, the study enrolled 3075 people aged 70 to 79 years, of whom 1584 (52%) were women and 1281 (42%) were black. Potential participants were recruited from a random sample of white and all black Medicare beneficiaries residing in designated ZIP code areas in Pittsburgh, PA, and Memphis, TN, with a mailed invitation followed by a telephone-screening interview to determine eligibility. Race was defined by self-report. Eligible participants should be free of disability in activities of daily living and free of functional limitation. Free of functional limitation defined as no difficulty walking a quarter of a mile, climbing one flight of stairs without resting, or performing basic activities of daily living. Persons with plans to leave the area within 3 years; who required an assistive device, such as a cane or walker; who reported being actively treated for cancer; or who were participating in a clinical or a lifestyle intervention trial were excluded.

Eligible participants were scheduled for a home interview during which eligibility was confirmed, consent was obtained, and a comprehensive interview was conducted followed by a clinic examination that included assessment of mobility and functional capacity. Centrally trained and certified technicians obtained the physical activity, physical function, and prevalent disease measures. The protocol was approved by the institutional review boards at the 2 field centers and the coordinating center. All participants gave written informed consent. At year 4, participants were asked to redo the LDCW test in order for their functional capacity to be re-evaluated. This analysis, however, includes data on 2935 participants; we excluded 140 participants with manifest HF at year 1. For outcomes, we used adjudicated 10-year follow up data. Data on functional capacity were available for 2576 participants.

4.3 Identification of the Critical Dependent and Independent Variables

The main independent variable (main exposure of interest) in the proposed project is functional capacity and cardiovascular response parameters at year 1, derived from the LDCW test. Specifically:

- Walking speed over 20 m – expressed as m/sec

- Distance covered in 2 min – expressed as m
- Walking speed over 2 min – expressed as m/sec
- Time needed to covered 400 m – expressed as sec
- Systolic blood pressure (SBP) and diastolic blood pressure (DBP) at the end of 400 m – expressed as mmHg
- Heart rate (HR) at the end of 2 min – expressed as beats/min
- HR at the end of 400 m – expressed as beats/min
- HR recovery – expressed as beats/min

Also, differences in functional capacity at year 4 versus year 1 will be evaluated. For this analysis, we will evaluate both the absolute parameters as described above and their absolute and relative changes from year 1.

The dependent variables (outcomes) of interest are:

- Mortality at 10 years

- Heart failure at 10 years

Because mortality rates in older adults can be substantially higher than the rates of incident heart failure, especially in the higher risk strata, and hence lead to overestimation of absolute risks (Koller, Raatz, Steyerberg, & Wolbers, 2012; Wolbers, Koller, Witteman, & Steyerberg, 2009), we will adjust for the competing risk of death in analyses looking at the association between functional capacity and HF. For this purpose, we will use extended Cox proportional hazards models (details will be provided in the statistical analysis section) (Koller et al., 2012; Wolbers et al., 2009). Finally, although HF can lead to death, we will use all-cause mortality in our primary analysis.

As previously discussed in Section 1 (Figure 3), there is a host of risk factors that can modify or confound the association between the exposure of interest (functional capacity) and outcomes. These risk factors have been identified from previous work done in the Health ABC Study and other large cohort studies. In the current study, these risk factors will be expressed through the covariates presented in **Table 1**.

4.4 Definition of the Proposed Outcome Measures

4.4.1 Outcome #1 – Mortality

The Health ABC Diagnosis and Disease Ascertainment Committee reviewed all deaths. For this purpose, the Committee reviewed hospital records, death certificates, and informant interviews.

4.4.2 Outcome #2 – Incident Heart Failure

All first admissions with an overnight stay that was confirmed as related to HF, based on symptoms, signs, chest radiograph results, and echocardiographic findings, using criteria similar to those used in the Cardiovascular Health Study, were designated as incident HF event (Fried et al., 1991). The criteria required HF diagnosis by a physician and treatment for HF (Rodondi et al., 2005). Briefly, an HF event was confirmed if, in addition to a physician diagnosis, there was documentation in the medical record of (a) symptoms (e.g., shortness of breath, fatigue), (b) physical signs (e.g., edema and rales), (c) supporting clinical findings (e.g., pulmonary edema on chest x-ray), and (d) treatment, including diuretics, digitalis, angiotensin-converting enzyme inhibitors or beta-blockers. Information from echocardiography was not required but was taken into account whenever available.

4.5 Analysis Plan

4.5.1 Univariate Analyses

For this analysis, we have excluded participants with prevalent HF or inconclusive or missing data on HF at baseline. To describe baseline characteristics and adjust for these characteristics in multivariable models, we will use values from the year 1 visit. We have opted to present the baseline characteristics (covariates) according the LDCW completion categories (excluded, stopped, completed) in order to facilitate clinical and public health interpretation. We will use the non-parametric test for differences across multiple categories (Kruskal-Wallis) to examine for differences of these characteristics across LDCW completion categories. The LDCW exercise performance parameters and cardiovascular response parameters at year 1 and year 4 will be analyzed as continuous variables.

4.5.2 Multivariable Analyses

Participants with contraindications for performing the test because of acute electrocardiogram abnormalities, abnormal vital signs (elevated blood pressure [≥200/110 mm Hg] or resting heart rate ≥120/min or ≤40/min), recent exacerbation of chest pain, shortness of breath, or a recent cardiac event or procedure were excluded. Therefore, the analysis of LDCW parameters refers to completers only. We will examine the association between (a) functional capacity parameters and cardiovascular response parameters at year 1 LDCW and (b) changes in these parameters from year 1 (baseline) to year 4 and outcomes (mortality and incident HF) by entering these parameters as continuous variables in appropriate proportional hazards models. For mortality, we will use Cox models. For HF, because of the considerably higher mortality rate that may inflate estimates especially for higher-risk patients, we will use the Fine and Gray extension of the Cox proportional hazards model (Fine & Gray, 1999). To identify potential nonlinear associations with the event of interest using the simulation approach available in the SAS 9.4 PROC PHREG module (ASSESS statement). We will then evaluate the proportional hazards assumption using the Schoenfeld residuals and interactions tests with time as appropriate. To graphically present crude survival and incidence HF according to completion categories, we will plot appropriate 10-year Kaplan-Meier curves and provide 10-year Kaplan-Meier estimates for survival and incidence of HF. We will compare the crude curves using the log-rank chi-square statistic.

In multivariable analyses, we will adjust for (i) clinical risk factors previously associated with mortality in the Health ABC Study (Newman et al., 2006); (ii) other factors that could affect functional capacity; and (iii) any additional covariates (i.e., baseline characteristics) from **Table 1** associated with the exposure of interest (functional capacity). The variables that will be used for adjustment are: age, gender, race, body mass index, smoking, self-reported physical activity, prevalent cardiovascular disease (coronary artery disease, cerebrovascular disease, and peripheral vascular disease), pulmonary disease, diabetes mellitus, hypertension, depression, systolic blood pressure, heart rate, electrocardiographic abnormalities, blood glucose, and serum levels of albumin, creatinine, and cholesterol. To examine for significant modification effects, we will introduce interaction terms in univariate models and verify in the multivariable model. We will only keep significant interaction terms in multivariable models.

To address the problem of missing covariate values, we will perform multiple imputation, assuming missingness at random. Multiple imputation method allows us to generate n data sets which have complete covariate data. We will then run multivariable regression models on each of the n data sets and pool the n sets of estimates. We will compare the pooled estimates with the original estimates to assess for bias as a sensitivity analysis.

To evaluate for potential multicollinearity among the adjustment covariates, we will construct a general linear model (PROC GLM) against an external variable (e.g. death occurrence) and evaluate for tolerance. We will consider tolerance ≤0.1 as an indicator of multicollinearity and re-evaluate the model.

In multivariable analyses, we will adjust for clinical risk factors previously identified as HF risk predictors in the Health ABC Study (Butler et al., 2008) and any additional covariates associated with functional capacity. Analyses were performed with STATA 13.1 (StataCorp LP, College Station, TX) and SAS 9.4 (SAS Institute Inc., Cary, NC).

4.6 Results

4.6.1 Descriptive Statistics

4.6.1.1 Study Population

Among the 2935 participants without manifest (prevalent) HF at baseline (i.e., after excluding 140 participants with definite or probable HF at baseline), 359 (12.2%) were excluded from taking the LDCW test. Among the 2576 participants who took the test, 331 (12.8%, or 11.3% of the participants without HF) did not complete the test. The baseline characteristics of participants according to LDCW completion status, i.e. excluded, stopped, and completed, are summarized and compared in **Table 1**.

Table 1. Baseline participant characteristics according to completion categories at baseline

Characteristic	Excluded	Stopped	Completed	P value*
N	**359**	**331**	**2245**	
Age, years	74.1 (2.9)	73.9 (2.9)	73.5 (2.8)	0.001
Male sex, N (%)	161 (44.8%)	110 (33.2%)	1136 (50.6%)	<0.001
Race				<0.001
Blacks, N (%)	185 (51.5%)	184 (55.6%)	846 (37.7%)	

Whites, N (%)	174 (48.5%)	147 (44.4%)	1399 (62.3%)	
Body mass index, kg/m^2	27.9 (5.4)	28.8 (5.8)	27 (4.5)	<0.001
Smoking				
Current smokers, N (%)	47 (13.1%)	42 (12.7%)	219 (9.8%)	
Past smokers, N (%)	162 (45.1%)	146 (44.1%)	1011 (45.0%)	
Physical activity, kcal/kg/week	73.9 (72)	76.3 (71)	86.2 (69)	<0.001
Hypertension, N (%)	194 (54.0%)	169 (51.1%)	901 (40.1%)	<0.001
Diabetes mellitus, N (%)	69 (19.2%)	67 (20.2%)	295 (13.1%)	<0.001
Left ventricular hypertrophy, N (%)	65 (18.1%)	42 (12.7%)	241 (10.7%)	<0.001
Coronary heart disease, N (%)	96 (26.7%)	65 (19.6%)	315 (14.0%)	<0.001
Cerebrovascular disease, N (%)	31 (8.6%)	34 (10.3%)	133 (5.9%)	<0.001
Peripheral vascular disease, N (%)	18 (5.2%)	36 (11.4%)	82 (3.7%)	<0.001
Any cardiovascular disease, N (%)	122 (34.0%)	89 (26.9%)	445 (19.8%)	<0.001
Pulmonary disease, N (%)	34 (9.5%)	14 (4.2%)	69 (3.1%)	<0.001
Depression, N (%)	52 (14.5%)	29 (8.8%)	224 (10.0%)	0.019
Systolic blood pressure, mmHg	143 (29)	138 (20)	135 (19)	<0.001
Diastolic blood pressure, mmHg	73.5 (15)	71.1 (11)	71.2 (11)	0.15
Heart rate, beats/min	68.3 (14)	68.5 (12)	64.4 (10)	<0.001
ECG – major abnormalities, † N (%)	113 (31.6%)	87 (26.3%)	422 (18.8%)	<0.001
ECG – minor abnormalities, ‡ N (%)	75 (21.1%)	60 (18.1%)	358 (16.0%)	0.064
Fasting Glucose, mg/dl	109 (45)	110 (40)	102 (31)	<0.001
Albumin, g/dl	3.97 (0.32)	3.97 (0.32)	3.98 (0.31)	0.70
Creatinine, mg/dl	1.09 (0.4)	1.07 (0.54)	1.04 (0.39)	0.047
Total cholesterol, mg/dl	203 (41)	207 (37)	203 (38)	0.16

Continuous variables are presented as mean (standard deviation); categorical variables are presented as number (%). ECG: electrocardiogram. * Nonparametric test for trend. † Major Q or QS abnormality, major ST or T wave abnormality, left ventricular hypertrophy, or ventricular conduction defects. ‡ Minor Q or QS abnormality or ST or T wave abnormalities.

As evident from Table 1, men, white, and participants with greater physical activity are more likely to complete the LDCW test. On the other hand, participants with hypertension, diabetes, and cardiovascular disease were more likely to stop before the completion of the test. Also, lower resting heart rate, systolic blood pressure (SBP), and presence of major or minor electrocardiographic abnormalities were associated with test completion, whereas no association was demonstrated for diastolic blood pressure (DBP).

4.6.1.2 Main Exposure

The distribution of the main exercise parameters and cardiovascular responses among those who completed the test are summarized graphically in **Figures 4-6**. The corresponding descriptive statistics are presented in **Table 2.**

Table 2. Summary of responses to LDCW test among completers (N=2245)

Response	Mean	SD	Median	Q1	Q3
Walking speed over 20m, m/sec	1.35	0.24	1.34	1.19	1.5
Distance covered at 2 min, m	155	26.2	155	138	173
Walking speed over 2 min, m/sec	1.29	0.22	1.29	1.15	1.44
Time to walk 400m - complete only, s	331	60.9	323	289	361
Standing SBP, mmHg	138	20.8	136	124	150
SBP at the end of 400 m, mmHg	149	24.4	148	132	164
Standing DBP, mmHg	76.7	13.0	78	70	86
DBP at the end of 400 m, mmHg	76.1	14.5	78	70	86
Resting heart rate, bpm	78.5	19.3	78	69	87
Heart rate at the end of 2 min, bpm	100	14.8	101	90	111
Heart rate at the end of the 400 m, bpm	104	15.3	104	93	115
Heart rate at min 2 of recovery, bpm	87.5	14.5	88	77	98

DBP: diastolic blood pressure; SBP: systolic blood pressure.

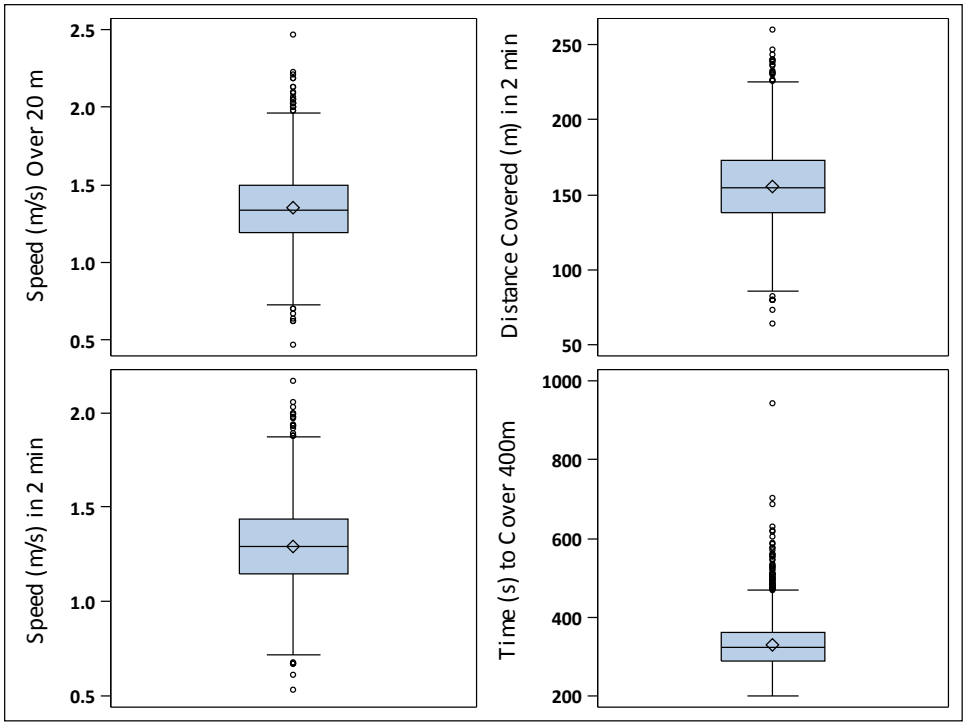


Figure 4. Main exercise responses to LDCW test.

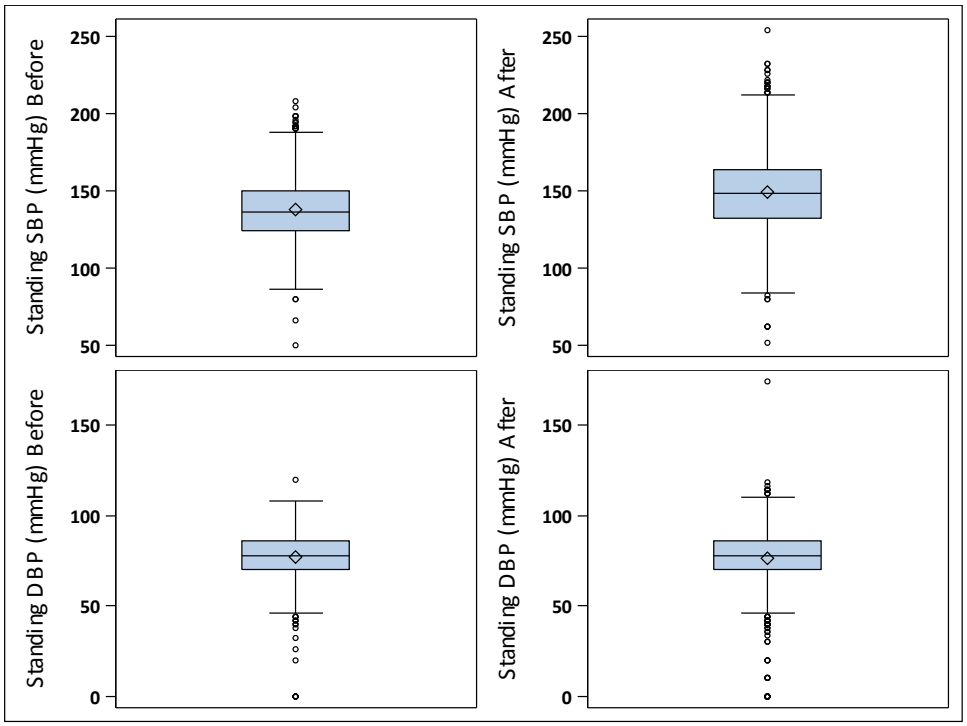


Figure 5. Blood pressure responses to LDCW test. SBP: systolic blood pressure; DBP: diastolic blood pressure.

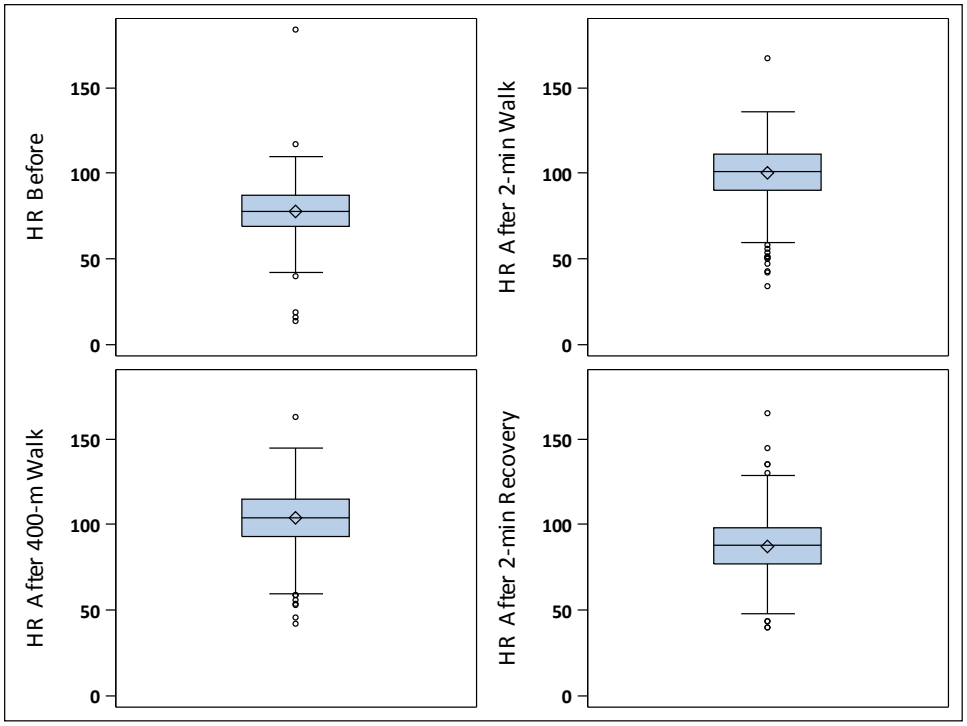


Figure 6. Heart rate responses to LDCW test. HR: heart rate;

Walking speeds over the first 20 m and in 2 min and the distance covered in 2 min were nearly symmetric, whereas time to cover 400 m is skewed to the right. In further analyses, the inverse of the time to 400m appear to be symmetric. Blood pressure and heart rate variables are also nearly symmetric for practical purposes.

4.6.2 Outcomes

4.6.2.1 Mortality

After 10 years of follow up, 620 of the 2245 (27.6%) participants who completed the test died as compared to 135 of the 331 (40.8%) who stopped the test and 151 of 359 (42.1%) who were excluded. The corresponding Kaplan-Meier estimates for 10-year mortality were 27.9% (95% CI, 26.1% to 29.8%), 41.1% (95% CI, 36.0% to 46.7%), and 42.4% (95% CI, 37.4% to 47.8%), respectively (log-rank χ^2=52.2; <0.001), **Figure 7**.

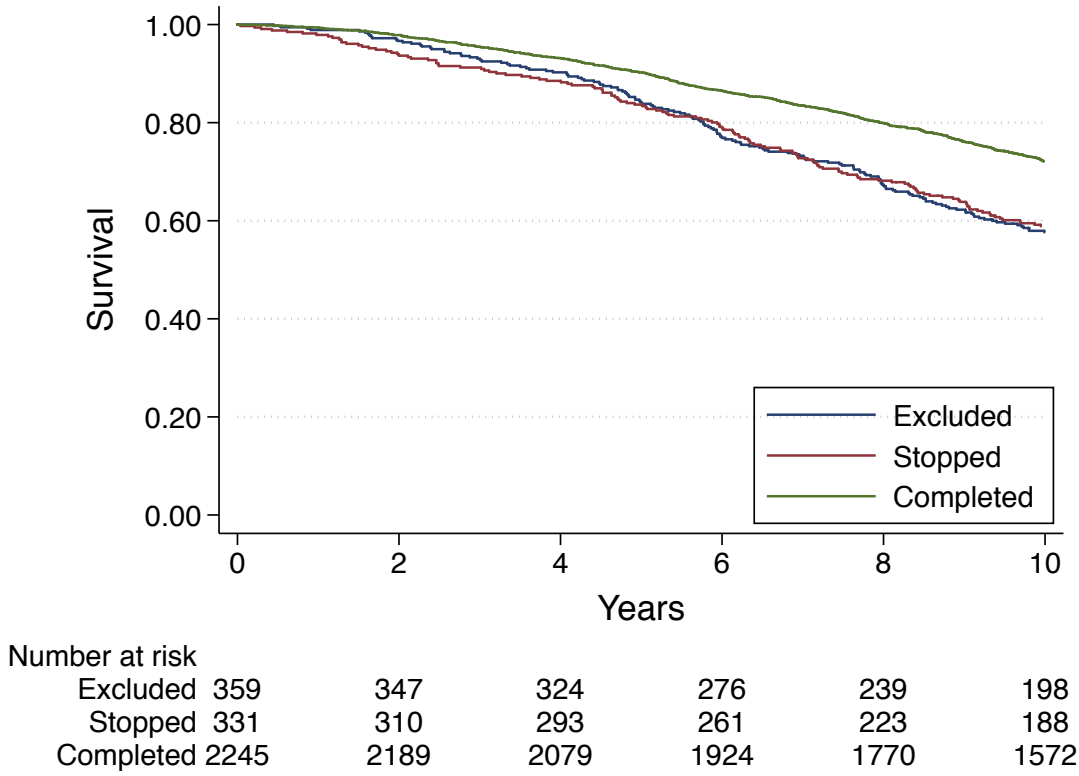


Figure 7. Mortality according to LDCW completion status.

In Cox proportional hazards models, the mortality HR for those who were excluded was 1.69 (95% CI 1.41–2.02; P<0.001) and for those who stopped was 1.64 (95% CI 1.36–1.98; P<0.001) with completers as the reference group. In multivariable models adjusting for the covariates described in **Table 1**, the increased risk persisted. The multivariable mortality HR for those who were excluded was 1.26 (95% CI 1.04–1.52; P=0.020) and for those who stopped was 1.48 (95% CI 1.22–1.81; P<0.001) with completers as the reference group.

4.6.2.2 Incident Heart Failure

After 10 years of follow up, 253 (11.3%) completers developed HF as compared to 63 (19.0%) among those who stopped the test and 82 (22.8%) among those who were excluded. The 10-year cumulative incidence estimates HF accounting for the competing risk of death were 11.4% (95% CI, 10.2% to 12.7%), 19.2% (95% CI, 15.8% to 23.3%), and 23.0% (95% CI, 18.9% to 27.9%), respectively, **Figure 8**.

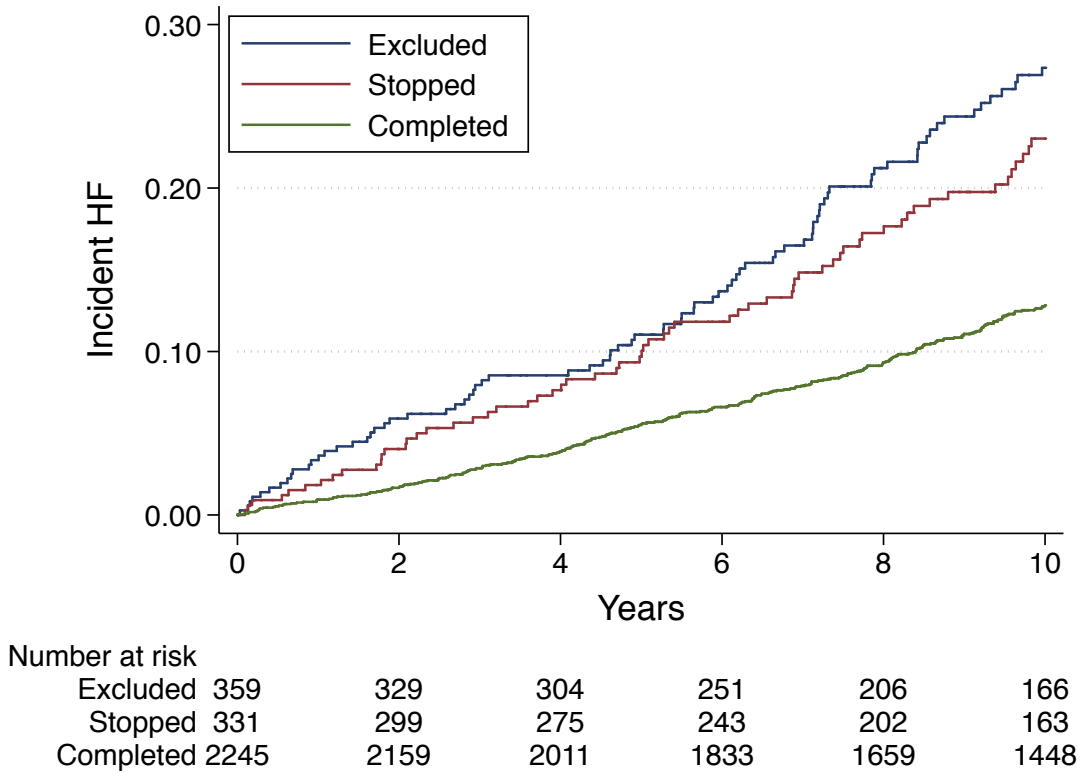


Figure 8. Incident heart failure according to LDCW completion status.

In proportional hazards models adjusting for the competing risk of death (Fine & Gray models), the sHR for HF those who were excluded was 2.17 (95% CI 1.69–2.79; P<0.001) and for those who stopped was 1.77 (95% CI 1.34–2.33; P<0.001) with completers as the reference group. In multivariable models adjusting for the covariates described in **Table 1**, multivariable HR for HF was 1.40 (95% CI 1.05–1.86; P=0.022) in those who were excluded and 1.34 (95% CI 0.99–1.82; P=0.059) in those who stopped with completers as the reference group.

4.6.3 Association of Exercise and Cardiovascular Responses with Outcomes

4.6.3.1 Mortality

We examined the univariate association of exercise and cardiovascular responses with 10-year mortality among completers (N=2245) by entering each variable in a univariate Cox proportional hazards model. For each variable, we also examined for appropriateness of the functional form and proportionality of hazards using the ASSESS statement and ZPH options, respectively, in PROC PHREG in SAS 9.4 (**Table 3**).

Table 3. Exercise and Cardiovascular Responses and Univariate Association with 10-year Mortality in Cox Proportional Hazards Models

Response	HR	Lower 95% CI	Upper 95% CI	P	Form*	PH†
Walking speed over 20m, per m/s	0.348	0.249	0.487	**<0.001**	0.21	0.42
Distance covered at 2 min, per m	0.990	0.987	0.993	**<0.001**	0.57	0.28
Walking speed over 2 min, per m/s	0.290	0.200	0.418	**<0.001**	0.79	0.28
Time to walk 400m, per s	1.004	1.003	1.005	**<0.001**	**<0.001**	0.65
Speed to walk 400 m, per m/s	0.219	0.149	0.322	**<0.001**	0.19	0.54
Standing SBP, per mmHg	1.001	0.997	1.006	0.52	0.57	0.64
SBP at the end of 400 m, per mmHg	1.001	0.998	1.004	0.62	0.33	0.50
Δ SBP, per mmHg	1.000	0.995	1.004	0.87	0.64	0.36
Standing DBP, per mmHg	0.998	0.991	1.005	0.41	0.29	0.48
DBP at the end of 400 m, per mmHg	1.003	0.997	1.009	0.30	0.20	0.54
Δ DBP, per mmHg	1.008	1.001	1.015	**0.025**	0.53	0.47
Resting heart rate, per bpm	1.003	1.000	1.006	**0.023**	0.10	0.77
Heart rate at the end of 2 min, per bpm	0.995	0.989	1.000	**0.044**	0.16	0.20
Δ Heart rate at 2 min, per bpm	0.986	0.980	0.993	**<0.001**	0.068	0.027
Heart rate at the end of 400 m, per bpm	0.995	0.990	1.001	0.079	0.13	0.097
Δ Heart rate at 400 m, per bpm	0.988	0.982	0.995	**<0.001**	0.28	0.011
Heart rate at 2 min of recovery, per bpm	1.003	0.998	1.009	0.25	0.034	0.61
Heart rate recovery,‡ per bpm	1.014	1.007	1.022	**<0.001**	0.057	0.064

* P value of the Kolmogorov supremum test based on 1000 simulations. Significant P values indicate inappropriate functional form. † P value for nonparametric correlation of Schoenfeld residuals with time. Significant P values indicate non-proportional hazards. ‡ Defined as heart rate 2 min after the test minus heart rate at 400 m. BPM: beats per minute; DBP: diastolic blood pressure; SBP: systolic blood pressure.

Because the results indicated that the association between time to walk 400 m and mortality was not linear (P<0.001 for the Kolmogorov supremum test), we have explored the variable and identified an inverse-normal distribution. The inverse transformation (=speed over 400 m in terms of interpretation) was indeed an appropriate form in Cox models for mortality (P=0.19 for the Kolmogorov supremum test), and therefore, we have used speed to walk 400 m

in subsequent models. The proportionality of hazards principle was met by almost all variables; for Δ heart rate at 2 min, Δ heart rate at 400 m, and heart rate recovery, the marginal non-proportionality was due to a few non-extreme outliers and we therefore considered the functional form as appropriate.

Among the LDCW test and the cardiovascular response parameters, strong predictors of mortality were the walking speeds to cover the first 20 m, during the first 2 minutes, and the 400-m. Resting heart rate, heart rate at the end of 2 minutes, heart rate at the end of the 400-m walk, and the differences from resting to heart rate at 2 min and 400 m and heart rate recovery were also univariate predictors of mortality.

In multivariate analyses, we evaluated those groups of variables that demonstrated significant signals, namely exercise responses, blood pressure responses, and heart rate-related variables. The results are summarized in **Table 4**.

Table 4. Exercise and Cardiovascular Responses and Multivariate Association with 10-year Mortality in Cox Proportional Hazards Models

Parameter	Adjusted HR*	Lower 95% CI	Upper 95% CI	P	PH†
Walking speed over 20 m, per m/s	0.417	0.280	0.621	**<0.001**	0.68
Distance covered at 2 min, per m	0.991	0.988	0.995	**<0.001**	0.69
Walking speed over 2 min, per m/s	0.348	0.226	0.537	**<0.001**	0. 69
Speed to walk 400 m, per m/s	0.257	0.161	0.411	**<0.001**	0.71
Δ SBP, per mmHg	0.998	0.993	1.003	0.47	0.47
Δ DBP, per mmHg	1.008	1.001	1.015	**0.036**	0.42
Resting heart rate, per bpm	1.002	0.998	1.006	0.40	0.62
Heart rate at the end of 2 min, per bpm	0.992	0.985	0.998	**0.016**	0.42
Δ Heart rate at the end of 2 min, per bpm	0.993	0.986	1.000	0.058	0.58
Heart rate at the end of 400 m, per bpm	0.994	0.987	1.000	**0.048**	0.29
Δ Heart rate at the end of 400 m, per bpm	0.995	0.989	1.002	0.17	0.48
Heart rate at 2 min of recovery, per bpm	0.998	0.991	1.006	0.61	0.36
Heart rate recovery,‡ per bpm	1.008	1.000	1.016	0.058	0.58

* Adjusted for variables in Table 2.† P value for nonparametric correlation of Schoenfeld residuals with time, global test. Significant P values indicate non-proportional hazards. BP: blood pressure; BPM: beats per minute, ‡ Defined as heart rate 2 min after the test minus the heart rate at 400 m.

All the parameters of the LDCW test retained their prognostic value for mortality after adjustment; however, the strongest parameter among them was the walking speed to cover the 400 meters. Heart rate at 2 min and at 400 m retained their prognostic value also.

Data on covariates were complete in 2175 out of 2245 participants (96.9%; missingness 3.1%). The only evident missing data pattern was among laboratory values (glucose, albumin, creatinine, cholesterol), which is plausible because of potentially unusable blood samples. Using 5 imputed datasets, we achieved relative efficiency (efficiency relative to an infinite number of imputations) of over >99.5% for all covariates. We then repeated the multivariable analyses above on the 5 imputed datasets and obtained pooled estimates. We observed that for all LDCW performance variables above, the pooled estimates from imputed datasets were similar to those obtained in the original dataset (deviation within the <2% range). Therefore, we did not proceed to multiple imputation analyses for the remaining multivariable analyses.

To assess for multicollinearity among adjustment covariates, we constructed a linear model (PROC GLM) with death as the outcome of interest and the adjustment covariates s predictors and evaluate for tolerance (type III tolerance). All tolerance factors were larger than 0.5 (corresponding to variance inflation factors [VIF] <2, since VIF=1/tolerance) and therefore we consulted that multicollinearity was not a problem with the adjustment model.

Finally, we tested for clinically important interactions between exercise parameters and cardiovascular responses and gender, race, and prevalent cardiovascular disease for mortality. We found that the response of systolic blood pressure to LDCW was differentially associated with 10-year mortality in men vs. women. Specifically, we observed that systolic blood pressure at the end of 400-m walk had an unadjusted hazard ratio of 0.996 per mmHg (95% CI 0.992-1.000, P=0.073) in men vs. 1.007 (95% CI 1.002-1.012, P=0.007) in women, P=0.001 for the interaction. This interaction persisted in adjusted models (P=0.018), although the corresponding adjusted hazard ratios were not statistically significant: 1.000 per mmHg (95% CI 0.994-1.005, P=0.86) in men vs. 1.003 (95% CI 0.996-1.009, P=0.45) in women. We did not detect any

significant interactions of the parameters of interest with race or prevalent cardiovascular disease for mortality.

4.6.3.2 Incident Heart Failure

We first examined the univariate association of exercise and cardiovascular response variables with 10-year incident HF among completers (N=2245) by entering each variable in competing-risks Fine & Gray models with death as the competing risk. The results are summarized in **Table 5**.

Table 5. Exercise and Cardiovascular Responses and Univariate Association with 10-year Heart Failure Incidence in Fine & Gray Proportional Hazards Models

Response	sHR	Lower 95% CI	Upper 95% CI	P
Walking speed over 20m, per m/s	0.366	0.222	0.606	**<0.001**
Distance covered at 2 min, per m	0.992	0.988	0.997	**0.001**
Walking speed over 2 min, per m/s	0.401	0.229	0.703	**0.001**
Speed to walk 400 m, per m/s	0.276	0.153	0.497	**<0.001**
Standing SBP, per mmHg	1.019	1.012	1.026	**<0.001**
SBP at the end of 400 m, per mmHg	1.013	1.008	1.018	**<0.001**
Δ SBP, per mmHg	1.000	0.993	1.007	**0.002**
Standing DBP, per mmHg	1.007	0.994	1.020	0.29
DBP at the end of 400 m, per mmHg	1.001	0.992	1.010	0.82
Δ DBP, per mmHg	0.991	0.981	1.001	0.086
Resting heart rate, per bpm	1.004	1.003	1.006	**<0.001**
Heart rate at the end of 2 min, per bpm	0.997	0.989	1.005	0.49
Δ Heart rate at the end of 2min, per bpm	0.990	0.980	1.000	**0.045**
Heart rate at the end of 400 m, per bpm	0.998	0.990	1.007	0.72
Δ Heart rate at the end of 400 m, per bpm	0.993	0.983	1.002	0.14
Heart rate at 2 min of recovery, per bpm	1.000	0.991	1.009	0.96
Heart rate recovery,[‡] per bpm	1.003	0.992	1.015	0.57

* P value of the Kolmogorov supremum test based on 1000 simulations. Significant P values indicate inappropriate functional form.

[†] P value for nonparametric correlation of Schoenfeld residuals with time. Significant P values indicate non-proportional hazards. BP: blood pressure; BPM: beats per minute.

All LDCW performance parameters, the standing systolic blood pressure (SBP), and SBP at the end of 400 m, as well as the difference of SBP from resting to the end of 400 m were strongly associated with incident HF in univariate models. Among the other cardiovascular response variables only resting heart rate and the difference of heart rate from resting to the end of 2 minutes were associated with incident HF.

In multivariate analyses, we evaluated those groups of variables that demonstrated significant signals, namely exercise responses, systolic blood pressure-related variables, and heart rate-related variables. The results are summarized in **Table 6**.

Table 6. Exercise and Cardiovascular Responses and Multivariate Association with 10-year Heart Failure Incidence in Fine & Gray Proportional Hazards Models

Response	Adjusted HR*	Lower 95% CI	Upper 95% CI	P
Walking speed over 20m, per m/s	0.517	0.284	0.939	**0.030**
Distance covered at 2 min, per m	0.996	0.991	1.002	0.20
Walking speed over 2 min, per m/s	0.652	0.342	1.245	0.20
Speed to walk 400 m, per m/s	0.522	0.257	1.057	0.071
Standing SBP, per mmHg	1.007	0.994	1.021	0.30
SBP at the end of 400 m, per mmHg	1.005	0.998	1.011	0.16
Δ SBP, per mmHg	1.000	0.993	1.007	0.97
Resting heart rate, per bpm	1.003	1.001	1.005	**0.006**
Heart rate at the end of 2 min, per bpm	0.994	0.984	1.004	0.25
Δ Heart rate at the end of 2min, per bpm	0.994	0.982	1.005	0.28
Heart rate at the end of 400 m, per bpm	0.996	0.986	1.007	0.50
Δ Heart rate at the end of 400 m, per bpm	0.997	0.987	1.008	0.26
Heart rate at 2 min of recovery, per bpm	0.993	0.980	1.006	0.26
Heart rate recovery,‡ per bpm	0.997	0.984	1.010	0.66

* Adjusted for variables in Table 2. † P value for nonparametric correlation of Schoenfeld residuals with time, global test. Significant P values indicate non-proportional hazards. BPM: beats per minute; DBP: diastolic blood pressure; SBP: systolic blood pressure

After adjustment, only the walking speed to cover the first 20 m and resting heart rate retain their prognostic value, which is in line with previous findings. The walking speed to cover 400 m did not seem to be associated with HF risk.

Finally, we tested for clinically important interactions between exercise parameters and cardiovascular responses and gender, race, and prevalent cardiovascular disease for incident HF. Similar to what we observed for mortality, we found that the response of systolic blood pressure to LDCW was differentially associated with 10-year HF in men vs. women. Specifically, we observed that systolic blood pressure at the end of 400-m walk had an unadjusted subhazard ratio of 1.009 per mmHg (95% CI 1.002-1.015, P=0.009) in men vs. 1.019 (95% CI 1.011-1.027, P<0.001) in women, P=0.040 for the interaction. However, this interaction did not persist in adjusted models (P=0.099). The corresponding adjusted subhazard ratios were 1.002 per mmHg (95% CI 0.994-1.011, P=0.57) in men vs. 1.009 (95% CI 1.000-1.019, P=0.063) in women. We did not detect any significant interactions of the parameters of interest with race or prevalent cardiovascular disease for incident HF.

4.6.4 Association Between Year 4 Exercise Responses and Outcomes

We evaluated both the absolute values in year 4 LDCW as well as the changes from the baseline test values as predictors of outcomes in the remaining 6-year horizon. Among the 2245 participants without HF who completed the test at baseline, 1418 (63.2%) have completed the year-4 test. **Table 7** summarizes both the responses and changes from year 1 (baseline).

Table 7. Summary of responses to LDCW test in year 4 among completers and changes from baseline LDCW test (N=1418)

Response	Mean	SD	Median	Q1	Q3
Distance covered at 2 min, m	162	27.2	160	143	181
Δ Distance covered at 2 min, m	1.84*	21.6	2.00	-11	15.0
Time to walk 400m, s	328	58.7	319	290	359
Δ Time to walk 400m, s	9.23 †	38.0	7.71	-11	28.5
Walking speed over 400m, m/s	1.25	0.21	1.25	1.11	1.38
Δ Walking speed over 400m, m/s	-.03 †	0.12	-.03	-.11	0.05

* NS from baseline. † P<0.001 from baseline

A mean increase of about 2 m was observed in the distance covered at 2 min, which was not statistically significant. However, the time needed to cover the 400 m significantly increased

by approximately 10 sec (P<0.001). Also, the walking speed to cover the 400 m was increased by approximately 0.03 m/sec (P<0.001).

4.6.4.1 Mortality

We examined the univariate association of functional capacity with mortality among completers (N=1418) by entering each variable in a univariate Cox proportional hazards model. Similarly, as above, for each variable, we also examined for appropriateness of the functional form and proportionality of hazards using the ASSESS statement and ZPH options, respectively, in PROC PHREG in SAS 9.4 (**Table 8**).

Table 8. Exercise and Cardiovascular Responses at Year 4 LDCW and Association with Subsequent 6-year Mortality in Cox Proportional Hazards Models

Response	HR	Lower 95% CI	Upper 95% CI	P	PH*
Distance covered at 2 min, per m	0.992	0.987	0.997	**0.001**	0.56
Δ Distance covered at 2 min, per m	0.994	0.989	1.000	**0.064**	0.93
Time to walk 400m, s	1.005	1.003	1.007	**<0.001**	0.38
Δ Time to walk 400m, s	1.005	1.002	1.009	**<0.001**	0.96
Walking speed over 400m, m/s	0.220	0.117	0.417	**<0.001**	0.50
Δ Walking speed over 400m, m/s	0.235	0.083	0.666	**0.006**	0.57

* P value for nonparametric correlation of Schoenfeld residuals with time. Significant P values indicate non-proportional hazards.

As evident from Table 8, the differences between the LDCW test parameters from year 1 to 4 were associated with mortality. Specifically, the difference in time needed to walk 400 m and the difference in walking speed over 400 m were strongly associated with mortality. For every additional second needed to cover 400 m, the risk of death increased by 0.5% (95% CI, 0.2% to 0.9%). Also, for a meter per sec increased walking speed over the 400 m, the risk of death decreased by 76% (95% CI, 33% to 92%).

4.6.4.2 Incident Heart Failure

We examined the univariate association of functional capacity variables with incident HF among year-4 completers (N=1418) by entering each variable in competing-risks Fine & Gray models with death as the competing risk. **Table 9** summarizes this association.

Table 9. Exercise and Cardiovascular Responses at Year 4 LDCW and Association with Subsequent 6-year Incident Heart Failure in Fine & Gray Proportional Hazards Models

Response	HR	Lower 95% CI	Upper 95% CI	P
Distance covered at 2 min, per m	1.000	0.992	1.008	0.94
Δ Distance covered at 2 min, per m	1.000	0.989	1.010	0.95
Time to walk 400m, s	1.001	0.997	1.004	0.70
Δ Time to walk 400m, s	1.002	0.997	1.007	0.54
Walking speed over 400m, m/s	0.880	0.314	2.468	0.81
Δ Walking speed over 400m, m/s	0.626	0.105	3.713	0.61

We concluded that exercise performance and changes from baseline were not associated with later incident HF in this population.

5 Journal Article

5.1 Introduction

Exercise capacity is an important indicator of health status and longevity (Gulati et al., 2005), reflecting the functional ability of several body systems. Conversely, impairment of exercise capacity indicates reduced function of one or more body systems. Aging causes declining of function of multiple systems, including the muscular (Nair, 2005), cardiovascular (Ferrari et al., 2003), and respiratory systems (Janssens et al., 1999), and reduced neuromuscular response times (Delbono, 2003), thus affecting exercise capacity. Reduced exercise capacity has been shown to be associated with increased risk for mortality in men and women, in whites and blacks, and in middle- and older age individuals (Blair et al., 1996; Blair et al., 1989; Gulati et al., 2003; Kokkinos et al., 2008; Mora et al., 2003; Myers et al., 2002; Sandvik et al., 1993; Sui, Laditka, et al., 2007). In addition, low exercise capacity has been associated with increased risk for hypertension (Barlow et al., 2006; Blair et al., 1984; Chase et al., 2009; Williams, 2008), diabetes mellitus (Sui et al., 2008; Wei et al., 1999; Williams, 2008), and cardiovascular events (Peterson et al., 2008). Similarly, the responses of the cardiovascular system during exercise capacity testing (e.g. heart rate and blood pressure response) strongly predict incident cardiovascular disease and mortality (Carnethon, Jacobs, Sidney, & Liu, 2003; Cole, Foody, Blackstone, & Lauer, 2000; Jouven et al., 2005; Lauer, Okin, Larson, Evans, & Levy, 1996; McHam, Marwick, Pashkow, & Lauer, 1999; Morshedi-Meibodi, Larson, Levy, O'Donnell, & Vasan, 2002; Singh et al., 1999; Vivekananthan, Blackstone, Pothier, & Lauer, 2003). However, the data on association of exercise capacity with risk for heart failure (HF) are limited, especially in older adults, who represent the population segment with the highest incidence and prevalence of HF (D. Lloyd-Jones et al., 2010).

Tests of varying complexity have been used to evaluate exercise capacity, ranging from the distance to be completed in a predefined time (e.g. the 6-min walk test [6MWT]) to simultaneous acquisition of several cardiovascular, ventilatory, and gas exchange variables (cardiopulmonary exercise testing). The latter provide pathophysiologic insights that are important for diagnosis (Sue & Wasserman, 1991), risk assessment (Sue & Wasserman, 1991), and decision-making (Sue & Wasserman, 1991); however, these tests cannot be widely performed due to the requirement of special equipment and expertise. Therefore, walking tests

have been introduced, allowing for wider implementation of exercise capacity testing and evaluation of patients, who are unable to complete complex protocols as a result of underlying comorbidities or age. The 6MWT is easy to perform, correlates strongly with oxygen consumption (Cahalin et al., 1995; Peeters & Mets, 1996), and has prognostic value in chronic conditions (Bittner et al., 1993; Casanova et al., 2008). However, 6MWT and its variants have some disadvantages, including a low test ceiling (Frost et al., 2005), subject motivation (Clark et al., 1994; Guyatt et al., 1984), and learning effects (Wu et al., 2003). To overcome these drawbacks, the long distance corridor walk test (LDCW), a two-stage, self-paced walking test similar to 6MWT, was introduced in the Health Aging and Body Composition (Health ABC) Study (Klepin et al., 2010; Simonsick, Montgomery, et al., 2001; Simonsick, Newman, et al., 2001; Simonsick et al., 2008). The LDCW helps older individuals approach their maximum capacity (Simonsick, Montgomery, et al., 2001), correlates strongly with oxygen consumption (Simonsick et al., 2006) and carries important prognostic information for mobility limitation and disability, cardiovascular disease, and all-cause mortality (Newman et al., 2006). However, the value of LDCW for HF risk prediction, and importantly, for refining HF risk assessment over simple clinical risk factors, has not been reported yet.

In this study, we investigate the association between LCDW parameters and risk for (1) all-cause mortality and (2) incident HF in the Health ABC Study using 10-year follow-up data. In secondary analyses, we will evaluate this association in gender and race subgroups and in participants with vs. without cardiovascular disease.

5.2 Methods

5.2.1 Study Population

The Health ABC is a community-based study of 3075 well-functioning individuals aged 70 to 79 years at inception, April 1997 and June 1998. Participants were recruited from a random sample of white Medicare beneficiaries and all age eligible black community residents in designated zip code areas surrounding Pittsburgh and Memphis. Exclusion criteria included difficulties with basic activities of daily living, obvious cognitive impairment, inability to communicate, anticipated move within 3 years, or participation in a trial involving lifestyle intervention. The institutional review boards at both sites and the coordinating center approved the study. At baseline and at year 4, participants were asked to undergo a test (LDCW) to

evaluate their exercise capacity. This analysis includes data on 2935 participants; we excluded 140 participants with manifest HF at year 1. Data on functional capacity were available for 2576 participants. For this analysis, adjudicated 10-year follow up data were used.

5.2.2 Assessment of Functional Capacity – Long Distance Corridor Walk

The LDCW test was used as an objective measure of participants' exercise capacity and also as a verification of their self-reported ability to walk a quarter of a mile, which is about 400 m. This test was conducted after enrollment and had 2 stages. Stage one was a 2-minute warm-up walk, where participants were instructed to cover as much distance as they could. Stage two was the 400-meter walk in a hallway on a 20-m per segment course for 10 laps (40 m per lap), where participants were instructed to walk as quickly as they could and at a pace that they could maintain. A standard encouragement was given at each lap. Heart rate was monitored continuously using the Polar Pacer (model 61190, Polar Electro, Inc., Oulu, Finland). Participants could stop the test because of fatigue or other symptoms. The staff stopped the test for persistent tachycardia (>135/min) by heart rate monitor. The distance covered in the 2-minute warm-up stage and the time needed for completion of the 400-m walk were recorded. Blood pressure and heart rate response, and heart rate recovery (change from heart rate at end of test until 2 minutes after) were also assessed.

5.2.3 Study Definitions

Race was self-defined by the participant. Diabetes mellitus was considered present if the participant reported a positive history or use of anti-hyperglycemic medication. Smoking was defined as current, past (≥100 lifetime cigarettes), or never. Physical activity was determined using a standardized questionnaire designed specifically for the Health ABC study, which was based on commonly used leisure-time physical activity assessments including the leisure-time physical activity questionnaire (Taylor et al., 1978). Briefly, participants were asked to report whether they had participated in a specific activity at least 10 times in the past 12 months and those who gave a positive answer were asked whether they had done this activity in the past 7 days; if so, they were asked to report the amount of time spent doing this activity. The amount of physical activity was calculated using the data of past 7 days. Kilocalories per week expended in common exercise activities (e.g., walking for exercise, exercise classes, weightlifting) and lifestyle activities (e.g., gardening, housework, yard work, non-exercise walking) were collected.

All physical activity data were calculated as kcal/wk by multiplying the appropriate kcal score for each of the activities by the amount of time spent during the week doing the activity (Ainsworth et al., 1993). Physical activity questionnaire generate information about total physical activity and exercise. Participants who reported at least 1000 kcal/week of formal exercise were defined as exercisers. Participants reported expenditure of no more than 2719 kcal/week of total physical activity were classified as sedentary and those reported expenditure of more than 2719 kcal/week of total physical activity were classified as having an active lifestyle (Brach, Simonsick, Kritchevsky, Yaffe, & Newman, 2004).

Cardiovascular disease status (including HF) at baseline was based on ICD 9-CM codes as reported by Medicare Services for the years 1995-1998; self-reported history; and medications. Prevalent CVD was defined as prevalent: (1) coronary heart disease (history of myocardial infarction, angina treated with medications, or coronary revascularization); (2) cerebrovascular disease (history of stroke, transient ischemic attack, or carotid endarterectomy); or (3) peripheral vascular disease (history of intermittent claudication or vascular bypass or angioplasty). These definitions follow the definitions used in previous Health ABC Study publications (Cesari et al., 2003; Newman et al., 2006). Incident CVD was defined as (1) incident coronary heart disease (myocardial infarction, angina, or coronary revascularization); (2) incident cerebrovascular disease (stroke, transient ischemic attack, or symptomatic carotid artery disease); (3) incident peripheral arterial disease; or (4) death due to cardiovascular causes.

Diabetes was defined as history of diabetes or use of antidiabetic medications. Hypertension was defined as use of antihypertensive medications and self-reported history or physician diagnosis of hypertension. Pulmonary disease was defined as use of medication (oral steroids, or any pulmonary medications including bronchodilators, inhaled steroids, theophylline and similar agents, antileucotrienes, and mast cell stabilizers) and self-reported history or physician diagnosed pulmonary disease. Presence of depression was defined as self-report of treatment for depression and use of an antidepressant or indication of antidepressant use in medications inventory, if there was no self-report of depression treatment. Left ventricular hypertrophy was determined from electrocardiography (Butler et al., 2008).

Major ECG abnormalities included: (1) atrioventricular conduction defect; (2) ventricular conduction defect; (3) rhythm irregularity; (4) left ventricular hypertrophy; (5) Q-wave; and (6) major T-wave and ST-segment abnormalities.

5.2.4 Study Outcomes

Participants were asked to report any hospitalizations they had and every 6 months they were contacted to elicit information about interim events. They were also asked direct questions regarding incident cardiovascular disease and HF events during the planned telephone interviews and in-person examinations. Medical records for overnight hospitalizations were reviewed at each site by local adjudicators; using algorithms mirroring those of the Cardiovascular Health Study, a panel of clinicians verified diagnoses and caused of death based on interview, review of all hospital records, and death certificates. All first admissions with an overnight stay that was confirmed as related to HF, based on symptoms, signs, chest radiograph results, and echocardiographic findings, using criteria similar to those used in the Cardiovascular Health Study, were designated as incident HF event (Fried et al., 1991). The criteria required HF diagnosis by a physician and treatment for HF (Rodondi et al., 2005). Briefly, HF was confirmed if there was documentation of (1) symptoms (e.g. shortness of breath, orthopnea) and signs (e.g. edema, pulmonary crackles); (2) supporting imaging findings (e.g. pulmonary edema on chest radiography); or (3) medical therapy for HF, including at least a diuretic and a vasodilator and/or digitalis. Left ventricular ejection fraction (LVEF) at HF diagnosis was not prospectively evaluated. Incident cardiovascular disease events were identified and adjudicated using the standard Health ABC Study surveillance and adjudication process described above. The Health ABC Diagnosis and Disease Ascertainment Committee reviewed all deaths.

5.2.5 Statistical Analysis

For this analysis, participants with prevalent HF or inconclusive or missing data on HF at baseline were excluded. Participants with contraindications for performing the test were excluded for the analysis of LDCW parameters – therefore, the analysis of LDCW parameters refers to completers only. To describe baseline characteristics and adjust for these characteristics in multivariable models, we will use values from the year 1 visit. We have opted to present the baseline characteristics (covariates) according the LDCW completion categories (excluded, stopped, completed) in order to facilitate clinical and public health interpretation. We will use the

non-parametric test for differences across multiple categories (Kruskal-Wallis) to examine for differences of these characteristics across LDCW completion categories. The LDCW exercise performance parameters and cardiovascular response parameters at year 1 and year 4 will be analyzed as continuous variables. We will examine the association between (a) functional capacity parameters and cardiovascular response parameters at year 1 LDCW and (b) changes in these parameters from year 1 (baseline) to year 4 and outcomes (mortality and incident HF) by entering these parameters as continuous variables in appropriate proportional hazards models. For mortality, we will use Cox models. For HF, because of the considerably higher mortality rate that may inflate estimates especially for higher-risk patients, we will use the Fine and Gray extension of the Cox proportional hazards model (Fine & Gray, 1999). To identify potential nonlinear associations with the event of interest using the simulation approach available in the SAS 9.4 PROC PHREG module (ASSESS statement). We will then evaluate the proportional hazards assumption using the Schoenfeld residuals and interactions tests with time as appropriate. Crude survival and incidence HF according to completion categories, will be presented using 10-year Kaplan-Meier curves and 10-year Kaplan-Meier estimates for survival and incidence of HF. We will compare the crude curves using the log-rank chi-square statistic.

In multivariable analyses, we will adjust for (i) clinical risk factors previously associated with mortality and incident HF in the Health ABC Study (Butler et al., 2008; Newman et al., 2006); (ii) other factors that could affect functional capacity; and (iii) any additional covariates (i.e., baseline characteristics) associated with the exposure of interest (functional capacity). Interaction terms will be used in univariate models and be verified in the multivariable model. We will only keep interaction terms if these retain significance in multivariable models. Analyses were performed with STATA 13.1 (StataCorp LP, College Station, TX) and SAS 9.4 (SAS Institute Inc., Cary, NC).

5.3 Results

5.3.1 Patient Baseline Characteristics

The mean age of participants (N=2935) was 73.6±2.9 years; 52.1% were women; and 41.4% were black and 58.6% were white. **Table 1** summarizes the baseline characteristics of these participants according to LDCW test completion category, i.e. those who were excluded, those who stopped, and those who completed the test. Median time needed to complete the 400

m was 323 sec (interquartile range [IQR], 289 to 361) **Table 2**. Men, men, white, and participants with greater physical activity are more likely to complete the LDCW test. On the other hand, participants with hypertension, diabetes, and cardiovascular disease were more likely to stop before the completion of the test. Also, lower resting heart rate, systolic blood pressure (SBP), and presence of major or minor electrocardiographic abnormalities were associated with test completion, whereas no association was demonstrated for diastolic blood pressure (DBP).

5.3.2 Outcomes

5.3.2.1 Mortality

After 10 years of follow up, 620 of the 2245 (27.6%) participants who completed the test died as compared to 135 of the 331 (40.8%) who stopped the test and 151 of 359 (42.1%) who were excluded. The corresponding Kaplan-Meier estimates for 10-year mortality were 27.9% (95% CI, 26.1% to 29.8%), 41.1% (95% CI, 36.0% to 46.7%), and 42.4% (95% CI, 37.4% to 47.8%), respectively (log-rank χ^2=52.2; <0.001), **Figure 1**.

5.3.2.2 Incident Heart Failure

After 10 years of follow up, 253 (11.3%) completers developed HF as compared to 63 (19.0%) among those who stopped the test and 82 (22.8%) among those who were excluded. The 10-year cumulative incidence estimates HF accounting for the competing risk of death were 11.4% (95% CI, 10.2% to 12.7%), 19.2% (95% CI, 15.8% to 23.3%), and 23.0% (95% CI, 18.9% to 27.9%), respectively, **Figure 2**.

5.3.3 Association of Functional Capacity and Outcomes

5.3.3.1 Mortality

In Cox models, the parameters of LDCW test were strongly associated with mortality. The unadjusted hazard ratio (HR) of these variables are shown in **Table 3** along with the P values that are indicative of variable function form and of proportional hazards. Because the results indicated that the association between time to walk 400 m and mortality was not linear (P<0.001 for the Kolmogorov supremum test), we have explored the variable and identified an inverse-normal distribution. The inverse transformation (=speed over 400 m in terms of interpretation) was indeed an appropriate form in Cox models for mortality (P=0.19 for the Kolmogorov supremum test), and therefore, we have used speed to walk 400 m in subsequent

models. The proportionality of hazards principle was met by almost all variables; for Δ heart rate at 2 min, Δ heart rate at 400 m, and heart rate recovery, the marginal non-proportionality was due to a few non-extreme outliers and we therefore considered the functional form as appropriate. Among the cardiovascular response parameters: (a) heart rate (i) at rest, (ii) at the end of 2 minutes, and (iii) at the end of the 400 meters, (b) the difference from resting heart rate to (i) heart rate at 2 min and (ii) at 400 m, and (c) heart rate recovery, were univariate predictors of mortality (**Table 3**).

This association was retained for all LDCW test parameters; the strongest parameter among them was the walking speed to cover 400 m. However, the association was attenuated in multivariable models for the majority of the cardiovascular response parameters (**Table 4)**.

5.3.3.2 Incident Heart Failure

The univariate association of exercise and cardiovascular response variables with 10-year incident HF among completers (N=2245) in competing-risks Fine & Gray models with death as the competing risk is presented in **Table 5**. All LDCW performance parameters, the standing systolic blood pressure (SBP), and SBP at the end of 400 m, as well as the difference of SBP from resting to the end of 400 m were strongly associated with incident HF in univariate models. Among the other cardiovascular response variables only resting heart rate and the difference of heart rate from resting to the end of 2 minutes were associated with incident HF.

In multivariate analyses, only the walking speed to cover the first 20 m and resting heart rate retain their prognostic value, which is in line with previous findings. The walking speed to cover 400 m did not seem to be associated with HF risk. The results are summarized in **Table 6**.

Finally, we tested for clinically important interactions between exercise parameters and cardiovascular responses and gender, race, and prevalent cardiovascular disease. We found that the response of systolic blood pressure to LDCW was differentially associated with 10-year mortality in men vs. women. Specifically, we observed that systolic blood pressure at the end of 400-m walk had an unadjusted hazard ratio of 0.996 per mmHg (95% CI 0.992-1.000, P=0.073) in men vs. 1.007 (95% CI 1.002-1.012, P=0.007) in women, P=0.001 for the interaction. This interaction persisted in adjusted models (P=0.018), although the corresponding adjusted hazard ratios were not statistically significant: 1.000 per mmHg (95% CI 0.994-1.005, P=0.86) in men

vs. 1.003 (95% CI 0.996-1.009, P=0.45) in women. We did not detect any significant interactions of the parameters of interest with race or prevalent cardiovascular disease.

5.3.4 Association Between Year 4 Exercise Responses and Outcomes

We evaluated both the absolute values in year 4 LDCW as well as the changes from the baseline test values as predictors of outcomes in the remaining 6-year horizon. Among the 2245 participants without HF who completed the test at baseline, 1418 (63.2%) have completed the year-4 test. **Table 7** summarizes both the responses and changes from year 1 (baseline). A mean increase of about 2 m was observed in the distance covered at 2 min, which was not statistically significant. However, the time needed to cover the 400 m significantly increased by approximately 10 sec (P<0.001). Also, the walking speed to cover the 400 m was increased by approximately 0.03 m/sec (P<0.001).

5.3.4.1 Mortality

We examined the univariate association of functional capacity with mortality among completers (N=1418) by entering each variable in a univariate Cox proportional hazards model. Similarly, as above, for each variable, we also examined for appropriateness of the functional form and proportionality of hazards using the ASSESS statement and ZPH options, respectively, in PROC PHREG in SAS 9.4 (**Table 8**). As evident from Table 8, the differences between the LDCW test parameters from year 1 to 4 were associated with mortality. Specifically, the difference in time needed to walk 400 m and the difference in walking speed over 400 m were strongly associated with mortality. For every additional second needed to cover 400 m, the risk of death increased by 0.5% (95% CI, 0.2% to 0.9%). Also, for a meter per sec increased walking speed over the 400 m, the risk of death decreased by 76% (95% CI, 33% to 92%).

5.3.4.2 Incident Heart Failure

We examined the univariate association of functional capacity variables with incident HF among completers (N=1418) by entering each variable in competing-risks Fine & Gray models with death as the competing risk. **Table 9** summarizes this association. We concluded that exercise performance and changes from baseline were not associated with later incident HF in this population.

5.4 Discussion

In our study, we did observe a strong association between functional capacity, assessed by the LDCW test, and mortality among the older adults participating in the Health ABC Study. All the various measures of LDCW performance, both for the first 2 min and the full 400-m test, were multivariate predators of mortality, the strongest being the speed to cover 400m. An association between functional capacity, and especially walking speed over the first 20 m and incident HF, was also observed in our study. Walking speed to cover the 400 m part of the test seems to be marginally associated with incident HF in this older population. Of note, differences in functional capacity from year 1 to 4 were not associated with mortality in multivariate models, although the absolute performance at year 4 was strongly associated with death over the next 6 years. Year 4 LDCW performance did not predict subsequent incident HF, perhaps reflecting selections bias since only relatively fit participant were still alive and able to take the year 4 test. To our knowledge this is the first study reporting on the association of both functional capacity and the temporal differences of functional capacity status with mortality and incident HF in a well-functioning older population.

The majority of data on the association between functional capacity and mortality are coming from studies evaluating maximal or submaximal exercise tests on treadmill or bicycle (laboratory tests). Although data on the association between functional capacity that has been assessed by walking tests (field tests) like LDCW test and mortality in healthy individuals are scarce, it has been shown that functional capacity assessed by walking tests is associated with mortality in this population (Newman et al., 2006; Yazdanyar et al., 2014). We also found that LDCW performance was predictive of mortality in older adults even after 10 years of follow-up. Walking tests are used more often in populations with chronic conditions like HF or chronic lung diseases. However, these tests could be used to adequately evaluate healthy individuals and especially older adults who may have difficulties to undergo a laboratory exercise test. Walking tests are inexpensive and easier to perform and they could be used more often in the clinical setting to evaluate healthy individuals or patients with chronic conditions.

Our findings of weak association between exercise performance and incident HF do not support the recently published data on the prognostic value of exercise performance on incident HF in middle-aged adults (Farrell et al., 2013; Khan et al., 2014). Although in these studies the

evaluation of the exercise capacity was done by laboratory tests (maximal exercise tests), and not by a field test as it was done in our study, this discrepancy cannot be attributed only to the different methods of exercise capacity evaluation. A possible explanation could be that the participants in the Health ABC study should have been well-functioning individuals by design. Also, considering that mortality is higher in this age group population than in middle-aged adults, the association of exercise capacity with HF is attenuated because of mortality. Physical inactivity with poor fitness leads to elevated levels of blood pressure and serum lipids, insulin resistance, and obesity, all of which predispose to the development of HF. On the other hand, regular physical activity may increase the capacity of endothelial cells to evoke vasodilatation in the early stages of atherosclerosis thus retarding its progression and prevent cardiovascular disease development (Hambrecht et al., 2000; Niebauer et al., 1997). Physical activity also protects against the development of cardiovascular diseases by having a favorable effect on risk factors of cardiovascular disease (Kraus et al., 2002; "Physical activity and cardiovascular health: Nih consensus development panel on physical activity and cardiovascular health," 1996; Roberts, Vaziri, & Barnard, 2002; Stewart, 2002; Stratton et al., 1991; Tran, Weltman, Glass, & Mood, 1983; Tuomilehto et al., 2001) and may help improve cardiac output, left ventricular function and oxygen utilization, and the formation of collateral vessels.(Hambrecht et al., 2000; Hinderliter et al., 2002; Myers et al., 2002) There are also suggestions that physical activity regulates cardiac autonomic function and vagal control of heart rate, therefore reducing risk of ventricular arrhythmias and subsequent risk of HF.(Tulppo, Makikallio, Seppanen, Laukkanen, & Huikuri, 1998) This is supported in our study also, since resting heart rate remained an independent risk factor for HF development. Considering the above data, confounding is also a possible explanation for the attenuated association of functional capacity and HF risk, since we have adjusted for several risk factors for HF that are associated with functional capacity.

In our population, there was a small decline in functional capacity over time, with an increase in time and a decline in walking speed to cover the 400 m part of the LDCW test . Although functional capacity status at year 4 was strongly associated with mortality, it was not associated with HF, a finding that supports our assumption that mortality may precede HF development in older adults and especially in those of higher risk – those with several prevalent risk factors – inducing selection bias over time.

There are several strengths and limitations in our study. Participants were well characterized. Also, the retention rate in the study was very high; thus, the potential bias because of loss-to-follow-up is limited. In our analysis, we included risk of death as a competing risk factor, to avoid inflation of estimates that could lead to incorrect interpretation of HF risk. Selection bias is inherent in our study because of design. Thus, our findings apply only to well-functioning older adults and may not be applicable to the general population of older individuals. Thus, careful interpretation is required for other older adult groups.

In conclusion, functional capacity as evaluated by a field test (LDCW) is strongly associated with mortality but less so with risk for HF. Similarly, temporal differences in functional capacity status were not associated with mortality or HF risk. However, because older adults have higher risk to die before developing HF, interventional studies to increase functional capacity may result in improved survival and better quality of life.

5.5 Tables

Table 1. Baseline participant characteristics according to completion categories at baseline

Characteristic	Excluded	Stopped	Completed	P value*
N	**359**	**331**	**2245**	
Age, years	74.1 (2.9)	73.9 (2.9)	73.5 (2.8)	0.001
Male sex, N (%)	161 (44.8%)	110 (33.2%)	1136 (50.6%)	<0.001
Race				<0.001
Blacks, N (%)	185 (51.5%)	184 (55.6%)	846 (37.7%)	
Whites, N (%)	174 (48.5%)	147 (44.4%)	1399 (62.3%)	
Body mass index, kg/m^2	27.9 (5.4)	28.8 (5.8)	27 (4.5)	<0.001
Smoking				
Current smokers, N (%)	47 (13.1%)	42 (12.7%)	219 (9.8%)	
Past smokers, N (%)	162 (45.1%)	146 (44.1%)	1011 (45.0%)	
Physical activity, kcal/kg/week	73.9 (72)	76.3 (71)	86.2 (69)	<0.001
Hypertension, N (%)	194 (54.0%)	169 (51.1%)	901 (40.1%)	<0.001
Diabetes mellitus, N (%)	69 (19.2%)	67 (20.2%)	295 (13.1%)	<0.001
Left ventricular hypertrophy, N (%)	65 (18.1%)	42 (12.7%)	241 (10.7%)	<0.001
Coronary heart disease, N (%)	96 (26.7%)	65 (19.6%)	315 (14.0%)	<0.001
Cerebrovascular disease, N (%)	31 (8.6%)	34 (10.3%)	133 (5.9%)	<0.001
Peripheral vascular disease, N (%)	18 (5.2%)	36 (11.4%)	82 (3.7%)	<0.001
Any cardiovascular disease, N (%)	122 (34.0%)	89 (26.9%)	445 (19.8%)	<0.001
Pulmonary disease, N (%)	34 (9.5%)	14 (4.2%)	69 (3.1%)	<0.001
Depression, N (%)	52 (14.5%)	29 (8.8%)	224 (10.0%)	0.019
Systolic blood pressure, mmHg	143 (29)	138 (20)	135 (19)	<0.001
Diastolic blood pressure, mmHg	73.5 (15)	71.1 (11)	71.2 (11)	0.15
Heart rate, beats/min	68.3 (14)	68.5 (12)	64.4 (10)	<0.001
ECG – major abnormalities, † N (%)	113 (31.6%)	87 (26.3%)	422 (18.8%)	<0.001
ECG – minor abnormalities, ‡ N (%)	75 (21.1%)	60 (18.1%)	358 (16.0%)	0.064
Fasting Glucose, mg/dl	109 (45)	110 (40)	102 (31)	<0.001
Albumin, g/dl	3.97 (0.32)	3.97 (0.32)	3.98 (0.31)	0.70
Creatinine, mg/dl	1.09 (0.4)	1.07 (0.54)	1.04 (0.39)	0.047
Total cholesterol, mg/dl	203 (41)	207 (37)	203 (38)	0.16

Continuous variables are presented as mean (standard deviation) or median (25th percentile, 75th percentile); categorical variables are presented as number (%). ECG: electrocardiogram. * Nonparametric test for trend. † Major Q or QS abnormality, major ST or T wave abnormality, left ventricular

hypertrophy, or ventricular conduction defects. ‡ Minor Q or QS abnormality or ST or T wave abnormalities.

Table 2. Summary of responses to LDCW test among completers (N=2245)

Response	Mean	SD	Median	Q1	Q3
Walking speed over 20m, m/sec	1.35	0.24	1.34	1.19	1.5
Distance covered at 2 min, m	155	26.2	155	138	173
Walking speed over 2 min, m/sec	1.29	0.22	1.29	1.15	1.44
Time to walk 400m - complete only, s	331	60.9	323	289	361
Standing SBP, mmHg	138	20.8	136	124	150
SBP at the end of 400 m, mmHg	149	24.4	148	132	164
Standing DBP, mmHg	76.7	13.0	78	70	86
DBP at the end of 400 m, mmHg	76.1	14.5	78	70	86
Resting heart rate, bpm	78.5	19.3	78	69	87
Heart rate at the end of 2 min, bpm	100	14.8	101	90	111
Heart rate at the end of the 400 m, bpm	104	15.3	104	93	115
Heart rate at min 2 of recovery, bpm	87.5	14.5	88	77	98

DBP: diastolic blood pressure; SBP: systolic blood pressure.

Table 3. Exercise and Cardiovascular Responses and Univariate Association with 10-year Mortality in Cox Proportional Hazards Models

Response	HR	Lower 95% CI	Upper 95% CI	P	Form*	PH†
Walking speed over 20m, per m/s	0.348	0.249	0.487	**<0.001**	0.21	0.42
Distance covered at 2 min, per m	0.990	0.987	0.993	**<0.001**	0.57	0.28
Walking speed over 2 min, per m/s	0.290	0.200	0.418	**<0.001**	0.79	0.28
Time to walk 400m, per s	1.004	1.003	1.005	**<0.001**	**<0.001**	0.65
Speed to walk 400 m, per m/s	0.219	0.149	0.322	**<0.001**	0.19	0.54
Standing SBP, per mmHg	1.001	0.997	1.006	0.52	0.57	0.64
SBP at the end of 400 m, per mmHg	1.001	0.998	1.004	0.62	0.33	0.50
Δ SBP, per mmHg	1.000	0.995	1.004	0.87	0.64	0.36
Standing DBP, per mmHg	0.998	0.991	1.005	0.41	0.29	0.48
DBP at the end of 400 m, per mmHg	1.003	0.997	1.009	0.30	0.20	0.54
Δ DBP, per mmHg	1.008	1.001	1.015	**0.025**	0.53	0.47
Resting heart rate, per bpm	1.003	1.000	1.006	**0.023**	0.10	0.77
Heart rate at the end of 2 min, per bpm	0.995	0.989	1.000	**0.044**	0.16	0.20
Δ Heart rate at 2min, per bpm	0.986	0.980	0.993	**<0.001**	0.068	0.027
Heart rate at the end of the 400 m, per bpm	0.995	0.990	1.001	0.079	0.13	0.097
Δ Heart rate at 400 m, per bpm	0.988	0.982	0.995	**<0.001**	0.28	0.011
Heart rate at 2 min of recovery, per bpm	1.003	0.998	1.009	0.25	0.034	0.61
Heart rate recovery,‡ per bpm	1.014	1.007	1.022	**<0.001**	0.057	0.064

* P value of the Kolmogorov supremum test based on 1000 simulations. Significant P values indicate inappropriate functional form.

† P value for nonparametric correlation of Schoenfeld residuals with time. Significant P values indicate non-proportional hazards.

‡ Defined as heart rate 2 min after the test minus the heart rate at 400 m.

BPM: beats per minute; DBP: diastolic blood pressure; SBP: systolic blood pressure.

Table 4. Exercise and Cardiovascular Responses and Multivariate Association with 10-year Mortality in Cox Proportional Hazards Models

Parameter	Adjusted HR*	Lower 95% CI	Upper 95% CI	P	PH†
Walking speed over 20 m, per m/s	0.417	0.280	0.621	**<0.001**	0.68
Distance covered at 2 min, per m	0.991	0.988	0.995	**<0.001**	0.69
Walking speed over 2 min, per m/s	0.348	0.226	0.537	**<0.001**	0. 69
Speed to walk 400 m, per m/s	0.257	0.161	0.411	**<0.001**	0.71
Δ SBP, per mmHg	0.998	0.993	1.003	0.47	0.47
Δ DBP, per mmHg	1.008	1.001	1.015	**0.036**	0.42
Resting heart rate, per bpm	1.002	0.998	1.006	0.40	0.62
Heart rate at the end of 2 min, per bpm	0.992	0.985	0.998	**0.016**	0.42
Δ Heart rate at the end of 2 min, per bpm	0.993	0.986	1.000	0.058	0.58
Heart rate at the end of 400 m, per bpm	0.994	0.987	1.000	**0.048**	0.29
Δ Heart rate at the end of 400 m, per bpm	0.995	0.989	1.002	0.17	0.48
Heart rate at 2 min of recovery, per bpm	0.998	0.991	1.006	0.61	0.36
Heart rate recovery,‡ per bpm	1.008	1.000	1.016	0.058	0.58

* Adjusted for variables in Table 2 (age, gender, race, body mass index, smoking, self-reported physical activity, prevalent cardiovascular disease [coronary artery disease, cerebrovascular disease, and peripheral vascular disease], pulmonary disease, diabetes mellitus, hypertension, depression, systolic blood pressure, heart rate, electrocardiographic abnormalities, blood glucose, and serum levels of albumin, creatinine, and cholesterol).

† P value for nonparametric correlation of Schoenfeld residuals with time, global test. Significant P values indicate non-proportional hazards. BPM: beats per minute; DBP: diastolic blood pressure; SBP: systolic blood pressure.

‡ Defined as heart rate 2 min after the test minus the heart rate at 400 m.

Table 5. Exercise and Cardiovascular Responses and Univariate Association with 10-year Heart Failure Incidence in Fine & Gray Proportional Hazards Models

Response	sHR	Lower 95% CI	Upper 95% CI	P
Walking speed over 20m, per m/s	0.366	0.222	0.606	**<0.001**
Distance covered at 2 min, per m	0.992	0.988	0.997	**0.001**
Walking speed over 2 min, per m/s	0.401	0.229	0.703	**0.001**
Speed to walk 400 m, per m/s	0.276	0.153	0.497	**<0.001**
Standing SBP, per mmHg	1.019	1.012	1.026	**<0.001**
SBP at the end of 400 m, per mmHg	1.013	1.008	1.018	**<0.001**
Δ SBP, per mmHg	1.000	0.993	1.007	**0.002**
Standing DBP, per mmHg	1.007	0.994	1.020	0.29
DBP at the end of 400 m, per mmHg	1.001	0.992	1.010	0.82
Δ DBP, per mmHg	0.991	0.981	1.001	0.086
Resting heart rate, per bpm	1.004	1.003	1.006	**<0.001**
Heart rate at the end of 2 min, per bpm	0.997	0.989	1.005	0.49
Δ Heart rate at the end of 2min, per bpm	0.990	0.980	1.000	**0.045**
Heart rate at the end of the 400 m, per bpm	0.998	0.990	1.007	0.72
Δ Heart rate at the end of the 400 m, per bpm	0.993	0.983	1.002	0.14
Heart rate at 2 min of recovery, per bpm	1.000	0.991	1.009	0.96
Heart rate recovery,[‡] per bpm	1.003	0.992	1.015	0.57

* P value of the Kolmogorov supremum test based on 1000 simulations. Significant P values indicate inappropriate functional form.

[†] P value for nonparametric correlation of Schoenfeld residuals with time. Significant P values indicate non-proportional hazards. BPM: beats per minute; DBP: diastolic blood pressure; SBP: systolic blood pressure.

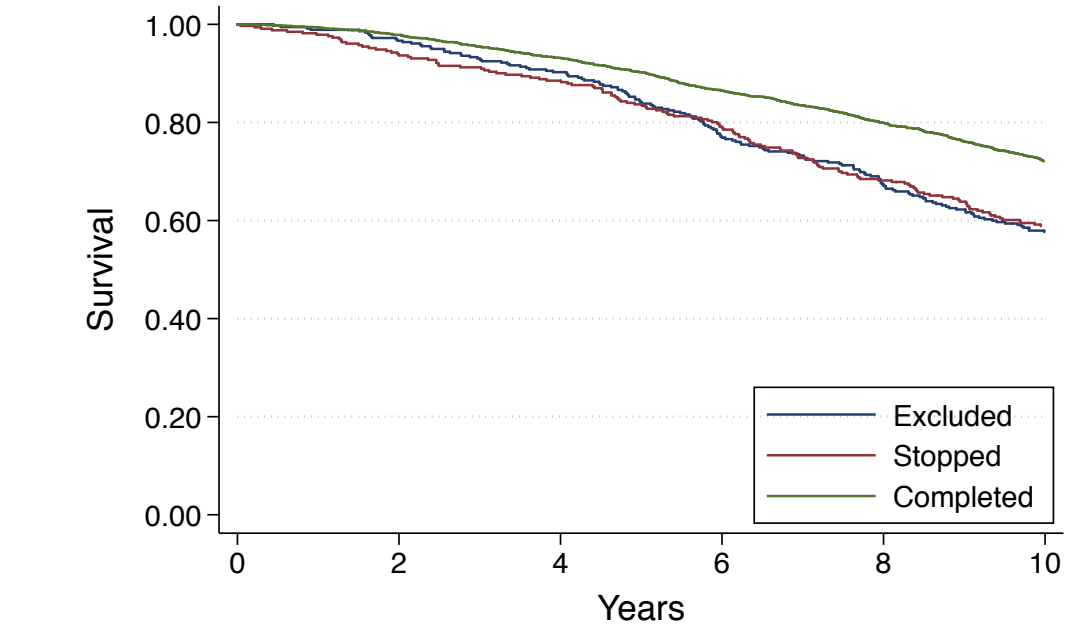
Table 6. Exercise and Cardiovascular Responses and Multivariate Association with 10-year Heart Failure Incidence in Fine & Gray Proportional Hazards Models

Response	Adjusted HR*	Lower 95% CI	Upper 95% CI	P
Walking speed over 20m, per m/s	0.517	0.284	0.939	**0.030**
Distance covered at 2 min, per m	0.996	0.991	1.002	0.20
Walking speed over 2 min, per m/s	0.652	0.342	1.245	0.20
Speed to walk 400 m, per m/s	0.522	0.257	1.057	0.071
Standing SBP, per mmHg	1.007	0.994	1.021	0.30
SBP at the end of 400 m, per mmHg	1.005	0.998	1.011	0.16
Δ SBP, per mmHg	1.000	0.993	1.007	0.97
Resting heart rate, per bpm	1.003	1.001	1.005	**0.006**
Heart rate at the end of 2 min, per bpm	0.994	0.984	1.004	0.25
Δ Heart rate at the end of 2min, per bpm	0.994	0.982	1.005	0.28
Heart rate at the end of 400 m, per bpm	0.996	0.986	1.007	0.50
Δ Heart rate at the end of 400 m, per bpm	0.997	0.987	1.008	0.26
Heart rate at 2 min of recovery, per bpm	0.993	0.980	1.006	0.26
Heart rate recovery,‡ per bpm	0.997	0.984	1.010	0.66

* Adjusted for variables in Table 2 (age, gender, race, body mass index, smoking, self-reported physical activity, prevalent cardiovascular disease [coronary artery disease, cerebrovascular disease, and peripheral vascular disease], pulmonary disease, diabetes mellitus, hypertension, depression, systolic blood pressure, heart rate, electrocardiographic abnormalities, blood glucose, and serum levels of albumin, creatinine, and cholesterol).

† P value for nonparametric correlation of Schoenfeld residuals with time, global test. Significant P values indicate non-proportional hazards. BPM: beats per minute; DBP: diastolic blood pressure; SBP: systolic blood pressure.

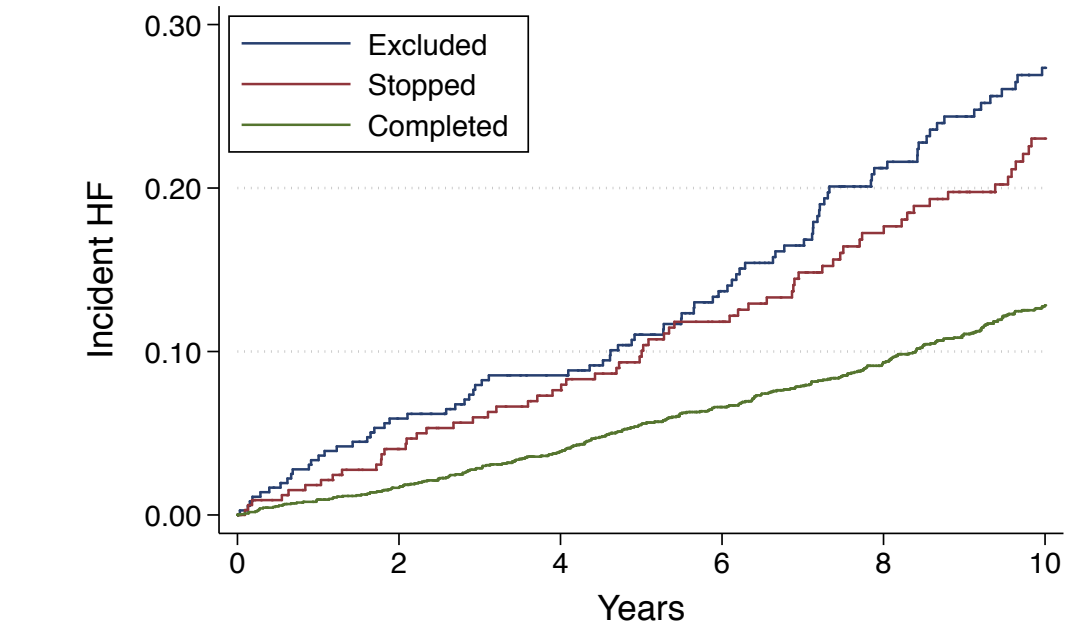
5.6 Figures



Number at risk

Excluded	359	347	324	276	239	198
Stopped	331	310	293	261	223	188
Completed	2245	2189	2079	1924	1770	1572

Figure 1. Mortality according to LDCW completion status.



Number at risk						
Excluded	359	329	304	251	206	166
Stopped	331	299	275	243	202	163
Completed	2245	2159	2011	1833	1659	1448

Figure 2. Incident heart failure according to LDCW completion status.

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