ASSOCIATION BETWEEN MEASURES OF AND PROGNOSTIC SIGNIFICANCE OF CARDIORESPIRATORY FITNESS IN COMMUNITY-DWELLING OLDER ADULTS

by

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The age structure of the U.S. population is expected to change with the segment of the population aged over 65 years experiencing the largest increase in size. Given the expected change in the U.S. population, efforts aimed at screening and diagnosis, in addition to the prevention and treatment of diseases with a significant burden in older adults should be at the forefront of public health efforts. Accordingly, in order to obtain an appreciation of the significance of cardiovascular diseases in older adults we initially performed a literature review of the burden and prevention of cardiovascular diseases, the leading cause of morbidity and mortality in older adults. Subsequently, we focused our research efforts on cardiorespiratory fitness in older adults. Cardiorespiratory fitness is a determinant of morbidity and mortality in middle-aged and older adults which can be measured objectively by either exercise testing or walk-based tests. Few studies of community-dwelling older adults have characterized the relationship between fitness as assessed by exercise testing versus walk-based testing, with subclinical cardiovascular, or the prognostic significance of walk-based test performance. We sought to characterize these relationships among community-dwelling adults participating in the Cardiovascular Health Study (CHS). In an analysis of the Arterial Calcification in the Elderly (ACE-CHS), 6 Minute Walk test (6 MWT) performance was a useful measure of treadmill test capability and performance. A second analysis of ACE-CHS failed to identify subclinical cardiovascular disease as quantified by the coronary artery calcification score as a significant

determinant of exercise duration in exercise treadmill testing. However, the coronary artery calcification score was associated with ischemia as detected by electrocardiographic changes during exercise testing. Finally, in the full CHS cohort, the 6 MWT performance was independently associated with all-cause mortality, demonstrating a prognostic value for submaximal fitness assessment using the 6 MWT across a wide range of function present in community-dwelling older adults. The public health relevance of these finding is the potential clinical utility of the 6 MWT, a quick, safe and inexpensive alternative to exercise treadmill testing, in the assessment of cardiorespiratory fitness and the prediction of mortality in community-dwelling older adults.

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1.0 INTRODUCTION

The age structure of the U.S. population is expected to change dramatically over the next 50 years with a nearly two-fold increase in the proportion of population aged ≥65 by year 2050[1]. While adults aged 65-84 years accounted for 10.9% of the total population in the year 2000, this proportion is estimated to increase to approximately 16% by year 2050. As for individuals aged ≥85 years, it is estimated this segment of the population will account for 5.0% of the total population in the year 2050, representing a greater than two-fold increase from that in the year 2000[2]. In terms of absolute numbers, given the concurrent projected growth of the overall population size, the number of adults aged ≥85 years is estimated to increase from approximately 4.3 million in the year 2000 to nearly 21 million by the year 2050[2]. The projected change in the U.S. age distribution is of public health significance in terms of burden from morbidity, mortality, and costs related to cardiovascular diseases.

The age-related increase in cardiovascular disease morbidity and mortality can be appreciated by consideration of the population-based disease-specific incidence and prevalence of cardiovascular diseases, including the overall cardiovascular disease, coronary heart disease, peripheral arterial disease, heart failure, valvular heart disease. Similarly, a review of measures of subclinical cardiovascular disease, such as age-associated changes in coronary artery calcification is insightful. The importance of the relationship between physical activity and fitness with age and also their association with morbidity and mortality will provide an important perspective of the public health impact of the aging U.S. population.

1.1 EPIDEMIOLOGY

In 2005 cardiovascular disease was the underlying cause in 864,480 out of approximately 2.5 million deaths of which adults aged ≥65 years accounted for the largest absolute numbers (Figure 1.1)[2]. In terms of morbidity, an estimated 80 million U.S. adults have at least one type of cardiovascular disease (CVD) and nearly one-half of which are aged ≥60 years[2]. In fact, there is marked increase in the incidence and prevalence of CVD with advancing age. The prevalence of CVD, including hypertension, coronary heart disease (CHD), heart failure (HF), and stroke, increases from about 40% in men and women 40-59 years of age, to 70-75% in persons 60-79 years of age, and to 79-86% among those aged 80 years or older (Figure 1.2)[2]. Similarly, the incidence of CVD, including CHD, HF, and stroke or intracerebral hemorrhage, increases from 4-10 per 1,000 person-years in adults aged 45-54 years to 65-75 per 1,000 person-years in adults aged 85-94 years (Figure 1.3)[2].

1.1.1 Cardiovascular Disease

In the United States, cardiovascular diseases account for more deaths than any other major causes of death with coronary heart disease and stroke accounting for approximately two-thirds of CVD deaths while the remaining CVD deaths are due to heart failure (7%), high blood pressure (7%), diseases of the arteries (4%), and other (14%)[2]. In 2005, approximately 80% of the 864,000 CVD deaths occurred in adults aged ≥65 years and nearly 40% of the CVD deaths occurred in adults aged ≥85 years[2]. In fact, the proportion of deaths due to CVD increases with advancing age. For instance, the 2004 percent of CVD deaths in US adults aged ≥85 years was 48% compared to 20% in those aged 35-44 years[2]. Comparison of 65-74 with 75-84 year old age groups reveals a nearly two-fold difference in the death rate due to HF, CHD, and stroke[2].

Although CVD is often thought to affect men more commonly than women, beyond approximately 60 years of age the prevalence of CVD is higher among women than men. In 2005, more than 200,000 of the 454,613 CVD deaths occurred in women aged ≥85 years compared to approximately 100,000 out of 409,867 CVD deaths observed in men aged ≥85 years[2].

1.1.2 Coronary Heart Disease

Coronary heart disease (CHD) is the most common form of CVD and accounts for more than half of all CVD-specific mortality. In 2005, CHD mortality accounted for a total of 445,687 CVD deaths of which the proportion accounted for by individuals aged ≥65 years was nearly 82%[2]. In both men and women, there is a marked increase in the prevalence of CHD with age (Figure 1.4)[2]. As for the incidence of CHD among older adults, the 10-year rate of MI increases with age among older adults aged ≥65 years regardless of race or gender (Figures 1.5 and 1.6)[2]. Even at the advanced age of 70 years, there still remains a 34.9% and 24.2% lifetime risk of a first coronary heart disease event in men and women, respectively[3].

1.1.2.1 Myocardial infarction

In addition to a poorer prognosis, Myocardial Infarction (MI) becomes more prevalent in old age as evident by a nearly seven-fold increase in MI prevalence comparing ages 35-44 to 65-74 years[4]. This pattern of age-related increase in MI prevalence extends into the oldest old age groups and by a greater magnitude in women. For instance, the MI prevalence in CHS women increased from 9.7% in adults aged 65-69 years to nearly 18% in women aged ≥85 years representing an increase of nearly two-fold in magnitude[5].

Annually, there are nearly half a million adults aged ≥75 years diagnosed with an MI[2]. Relative to the younger age group 35-44 years, men and women aged 65-74 years have an approximately ten- and an approximately 6-fold increase in the incidence rate MI, respectively. This represents an increase from approximately 1.0 to nearly 10 per 1,000 person years in men. For CHS women, the incidence rate increased from 0.3-0.7 to 5.1-7.2 per 1,000 person-years when comparing age groups of 35-44 to 65-74 years[6]. Data from CHS shows that the age-related increase in MI incidence continues into oldest age groups as evident by a two- and three-fold increase in the incidence rate of MI from the age of 65-69 to the oldest age groups (Figures 1.7 and 1.8)[6].

As for the prognosis of an MI in older adults, it is associated with both a poor short- and long-term prognosis as reflected by a likelihood of recurrent MIs and mortality[2, 7]. Adults aged ≥75 years with history of MI have a nearly 1.5-2-fold increased likelihood of recurrent MI, stroke, and heart failure when compared with those aged 40-69 years[2]. Likewise, in terms of mortality, individuals aged ≥75 years with a history of MI have a 1.5-fold increased 5-mortality when compared to adults aged 40-69 years[2].

1.1.3 Heart Failure

In 2005, heart failure (CHF), a disease of the predominantly older adults, was the underlying cause of approximately 59,000 deaths and mentioned on nearly 300,000 U.S. death certificates[2, 8]. The aging population combined with improved survival from comorbid conditions, such as coronary heart disease and hypertension, have led to an increase in both the prevalence and incidence of heart failure. While heart failure is relatively uncommon in adults aged 20-39 years with a prevalence of 0.1-0.2%, its prevalence increases to 5-10% in adults aged 60-79 years, and 12-14% by age ≥80 years[2]. Among community-dwelling older adults, the 18% prevalence of CHF in CHS men aged ≥85 years is higher than the 12% prevalence observed in men in the younger age group of 66-69 years. Likewise in CHS women aged 66-69 years, the 6% prevalence of CHF is less than half of the 14% prevalence observed in women aged ≥85 years[9].

In addition to the high prevalence of CHF, older adults free of prevalent CHF continue to have an approximately 1 in 5 lifetime risk for incident CHF[9]. For instance, men aged 80 years free of prevalent CHF have a 20.2% risk for developing CHF which is close to the 21.0% lifetime risk for 40 year old men. However, unlike the case of younger adults, the risk in older individuals is much greater in the short term. For instance, while the 5-year risk of CHF for an 80 year old is around 8%, the risk for a 40 year old is much lower at approximately 0.2%.

According to CHS data, the 10-year incidence rate of CHF in older adults 65 years and older increases up to six-fold across age strata[6]. There is a three- and six-fold increase in the incidence rate of CHF by age 85 years and older in Caucasian men and women, respectively (Figure 1.9)[6]. Similarly, in African American men and women, there is an approximately three-fold increase in the incidence rate of CHF across age strata (Figure 1.10)[6]. In both Caucasian and African Americans, older men have a higher overall 10 year incidence rate of CHF than women participating in the Cardiovascular Health Study. While the incidence rate of CHF in adults aged ≥65 years is higher in Caucasian men than in African Americans, the reverse is true for CHF incidence with respect to race in women (Figures 1.9 and 1.10)[6].

1.1.4 Stroke

Stroke is the third leading cause of death and a leading cause of long-term disability in the U.S. While the prevalence of stroke is below 3% in adults aged 20-59 years, it increases to approximately 8% by age 60-79 years, and reaches 13-17% for adults aged ≥80 years[2].

The overall 10-year incidence rate for stroke in CHS men and women range from 13.7-14.7 per 1,000 person-years[6]. In the CHS cohort of older adults aged ≥65 years, the overall 10-year incidence rate in African American women is higher than in Caucasian women. In contrast, the overall 10-year incidence of strokes is higher in older Caucasian men than in African American men[6]. Similar to many other common CVD types, the incidence of stroke increases with age. The stroke incidence rate increases two- to five-fold across advancing age groups (Figures 1.11 and 1.12)[6].

1.1.5 Peripheral Arterial Disease

Peripheral arterial disease (PAD) is a significant predictor of cardiovascular and overall mortality. In addition, PAD has been shown to be associated with limitations due to physical function inversely related to health-related quality of life[10, 11]. Peripheral Arterial disease, as measured by an ankle brachial index (ABI) <0.9, was found to be present in 12.4% of 5,084 CHS participants[12]. In a cohort of CHS participants free of prevalent CVD, there was nearly a three-fold increase in the prevalence of men with ABI<0.9 with advancing age reaching a prevalence of approximately 30% in men aged ≥85 years[12]. Similarly, in CHS women free of prevalent CVD, the prevalence of ABI<0.9 was nearly 40% in participants aged ≥85 years which is approximately eight-fold higher than the prevalence in women aged 65-69 years[12].

1.1.6 Valvular Heart Disease

In 2005, diseases of the heart valves accounted for 93,000 hospital discharges and nearly 21,000 deaths out of which approximately 13,000 were due to aortic valve disease[2]. The prevalence of aortic stenosis (AS), defined as thickened leaflets with reduced systolic openings on two dimensional imaging and an increased anterograde velocity (≥2.5 m/s by continuous wave Doppler ultrasound), increases across advancing age groups among elderly participants of the Cardiovascular Health Study. While the prevalence AS is 1.3% in adults aged 65-74 years, by age 75-84 years the prevalence increases nearly two-fold to 2.4%, and the prevalence of AS reaches 4% among adults aged ≥85 years[13].

The Healthy Ageing Study reported on the prevalence of aortic valve abnormalities by severity of stenosis using ultrasound recordings of 552 participants[14]. The age distribution ranged from 51 to 86 years consisting of a sample size of 197 participants aged 75-76 years, 155 participants aged 80-81 years, and 124 participants aged 85-86 years. By accounting for the possibility of a narrow left ventricular outflow tract found in the elderly, these investigators defined aortic stenosis based on a calculated velocity ratio≤0.35 in combination with a calculated aortic valve area (AVA) ≤1.2 cm^2 for moderate and AVA ≤0.8 cm^2 for critical aortic valve stenosis. Based on this definition of AS, the overall prevalence of at least moderate and critical aortic stenosis in adults aged 75-86 years were 4.8% and 2.9%, respectively. There is an increase in the prevalence of both of these categories of AS with age. The prevalence of at least moderate severity aortic stenosis increased from 2.5% for adults aged 75-76 years, to 3.9% in 80-81 years old, and 8.1% by ages 85-86 years. The prevalence rates for critical aortic stenosis for these same age groups categories was reported to be 0.5%, 2.6%, and 5.6%, respectively.

1.1.6.1 Valvular Regurgitation

The prevalence of valvular regurgitation, including mitral, tricuspid, and of aortic valves, was determined for participants aged 26 to 83 years in the Framingham Heart Study[15]. The prevalence of valvular regurgitation abnormalities, assessed using color Doppler echocardiography, increases with age in both genders. In men, the prevalence of at least mild severity mitral regurgitation increases nearly four-fold from 8.9% in adults aged 26-39 years to 39.3% in adults aged 70 – 83 years. The prevalence of at least mild tricuspid regurgitation in men increases more than two-fold from 13.0% in adults aged 26-39 years to 27.3% in adults aged 70-83 years. Similarly, the prevalence of aortic valve regurgitation in men increases from 0% in 26-39 year olds to 14.4% in men aged 70-83 years. The prevalence of at least mild degree of mitral, tricuspid, and aortic valve regurgitation in women aged 26-39 years are 9.7%, 14.4%, and 0%, respectively. By ages 70-83 years, these prevalence rates increase to 23.6%, 29.5%, and 16.9%, respectively. The age-related increase in the prevalence of various types of valvular heart disease has been confirmed by a pooled analysis of echocardiography data from 11,911 participants of the three epidemiologic studies of Coronary Artery Risk Development in Young Adults (CARDIA), Atherosclerosis Risk in Communities (ARIC), and the Cardiovascular Health Study[16].

In contrast to the other forms of valvular heart diseases, the prevalence of mitral valve prolapse (MVP) has not been observed to vary significantly with age[17]. Based on data from

3491 Framingham Heart Study participants with mean age 54.7 (Range: 26 to 84 years), the overall prevalence of MVP is 2.4%. The prevalence of MVP did not vary significantly across advancing decades of age from the age of 30 to 80 years.

1.1.7 Atrial Fibrillation and Other Electrocardiogram Abnormalities

1.1.7.1 Atrial Fibrillation

While the prevalence of atrial fibrillation (AF) was estimated to be 2.2 million in 2005, it is projected that by 2050 the number of individuals with AF will exceed 10 million[2, 18]. In participants of CHS, the overall prevalence of AF in men and women was observed to be 6.2% and 4.8%, respectively[19]. The prevalence of AF varied by cardiovascular disease status, such that the prevalence was 8.7% in men with clinical CVD, 4.5% with subclinical CVD, and 1.1% in men without known cardiovascular disease[19]. The prevalence of AF in women with clinical was 9.4%, 4.7% with subclinical CVD, and 2.7% in women without cardiovascular disease[19]. Regardless of CVD status, the prevalence of AF increased with age such that the prevalence increased from 2.8% in women aged 65-69 years to 6.7% in women aged ≥80 years[19]. Similarly in men aged 80 years and older the prevalence of atrial fibrillation of 8.0% was higher than the 5.9% observed in men aged 65-69 years[19].

The lifetime risk for atrial fibrillation in adults without known CHF or MI remains approximately 15% in adults aged 40 years as well as in individuals aged 80 years[20]. The overall incidence rates of atrial fibrillation in elderly participants of the Cardiovascular Health Study were 26.4 and 14.1 per 1,000 person-years, for men and women respectively[21]. There is an age associated increase in the incidence of AF in both genders such that the incidence of 12.3 person years in men aged 65-69 years increases to 58.7 per 1,000 person-years by the age ≥80 years.

Similarly, the incidence rate of atrial fibrillation in women increases from 10.9 per 1,000 person-years in women aged 65-69 years to 25.1 per 1,000 person-years in women aged ≥80 years[21].

1.1.7.2 Abnormalities of the Electrocardiogram

Resting Electrocardiogram (ECG) abnormalities are quite common in older adults. Evaluation of the ECGs from 5,150 CHS participants revealed an overall prevalence of any ECG abnormality to be 28.7%[22]. The prevalence rate for the presence of any ECG abnormality increases across age groups from 16.0% in men aged 65-69 years, to 27.5% by age 75-79 years, and 45.9% by age ≥85 years[22]. Similarly in women the prevalence of ECG abnormalities increases across age groups from 10.5% in age 65-69 years, to 20.2% by age 75-79 years, and 31.6% by age ≥85 years[22]. The observed prevalence, from most common to least, of the different types of ECG abnormalities, are 8.7% for ventricular conduction defects, 5.3% for first-degree atrioventricular block, 3.2% for atrial fibrillation, 6.3% for isolated major ST-T wave abnormalities, 4.2% for left ventricular hypertrophy, and 5.2% for major Q/QS waves[22]. The most common among the ventricular conduction defects was a Right Bundle Branch Block with a prevalence of 4.3%, followed by intraventricular block of indeterminate type at 2.7%, followed by a prevalence of 1.7% for Left Bundle Branch Blocks[22].

Twenty-four hour ambulatory electrocardiography has been evaluated in 1,372 CHS participants and revealed that the presence of minor supraventricular arrhythmias or any supraventricular ectopic beats is extremely common in the elderly and observed in approximately 97% of older adults[23]. Only 2.8% of elderly CHS participants were free of supraventricular arrhythmias and only 18% were without any ventricular ectopic activity[23]. Frequent ectopic beats, defined as ≥15 beats per hour, were recorded in nearly half of men and women and were more commonly of supraventricular origin. Although less common, ventricular ectopic beats were observed in 57.1% and 55.5% of men and women, respectively[23]. The prevalence rates for ventricular tachycardia, defined as ≥3 complexes, were 13% and 4.3% in men and women, respectively[23]. Supraventricular tachycardia, defined as ≥3 complexes, was seen in 47.7% and 49.9% of men and women, respectively[23]. There is an age-related increase in the prevalence of supraventricular arrhythmias and by age ≥80 years is observed in more than three-quarters of subjects[23]. However, serious arrhythmias including sustained ventricular tachycardia (≥15 complexes) and complete atrioventicular blocks were rarely detected (≤0.5%) in community-dwelling older adult participants of CHS[23].

1.1.8 Subclinical Cardiovascular Disease

The presence of various types of subclinical CVD can be measured by noninvasive methods such as the ankle-arm blood pressure, carotid ultrasound of carotid arteries, and an electrocardiogram, Magnetic Resonance Imaging of the brain, and Computed Tomography scanning of the heart and coronary arteries. The prevalence of such subclinical CVD increases with age[24]. For example, the prevalence of brain white matter changes and coronary artery calcium score increase progressively with age in both men and women[25-27]. In the case of subclinical peripheral arterial disease in CHS participants, defined as AAI<0.9, the prevalence increased approximately three and 8-fold from the age 65-69 years to those aged ≥85 years in women and men, respectively. In addition to being of prognostic significance, the presence of subclinical disease impacts physical and cognition function. In CHS, for example, compared to people 65 years of age or older with a normal ABI (i.e., ≥ 0.9), those with an ABI < 0.8 had a 3.5-fold increased risk of frailty[28]. Alternatively viewed, the presence of subclinical CVD among participants in CHS was associated with a loss of approximately 6.5 years of "successful" life (i.e. with good health and function) in women and 5.6 years in men[29].

1.1.8.1 Calcification of the Heart Structures

Calcification of the cardiac structures, a marker of increased CVD risk, is commonly detected in older adults[30]. For example, a necropsy study of 490 cases aged ≥80 years found that calcified deposits were present in 91%[31]. The calcification of the heart structures varies in location, including the coronary arteries, aortic valve cusps, mitral valve annulus, and the left ventricular papillary muscles, and is of prognostic significance[32].

Calcification of the aortic valve is a common finding in advanced age[13, 14]. In adults, it is present in 53% of the adults over the age of 55 years while there was a decrease in the proportion free of any valvular calcification with advancing age[14]. While 72% of persons aged 55-71 years were found to be without aortic valve calcification in persons aged 55-71 years, this proportion decreased to only 25% of individuals aged 85-86 years. The prevalence of slight aortic valve calcification increases nearly three-fold from 21% in 55-71 year olds to 56% in adults aged 85-86 years. Similarly, the prevalence of severe aortic valve calcification increases from 7% in 55-71 year olds to 19% in persons aged 85-86 years.

In addition to valvular calcification, sclerosis of the valve has been shown to be present and carry prognostic importance. Aortic valve sclerosis, defined as increased echogenicity and leaflet thickness without restriction of leaflet motion, is associated with an increase of approximately 50% in the risk of CVD death and incident MI[33]. Aortic valve sclerosis was reported to have an overall prevalence of 26% in CHS participants[13]. The sclerosis of the aortic valve increases in prevalence from 20% in 65-74 year olds, to 35% in 75-84 year olds, and reaches 48% for adults aged ≥85 years.

Mitral Annular Calcification (MAC), a degenerative calcification of the mitral valve support ring, has been shown to be independently associated with 1.5- to two-fold increase in risk of incident stroke and other CVD events, CVD- and all-cause mortality[34,35]. The relationship between mitral annular calcification with advancing age has been observed in a number of clinical and autopsy studies. Similar age-related increases in the presence of MAC have been found in epidemiological studies, including the Cardiovascular Health Study and the Framingham Heart Study (FHS), regardless of mode of MAC detection.

Mitral annular calcification (MAC), defined as an intense echocardiograph-producing structure located at the junctions of the atrioventricular groove and posterior mitral leaflet on the parasternal long-axis, apical 4-chamber, or parasternal short-axis view, was assessed using two-dimensional echocardiography in CHS participants and found to have an overall prevalence of 42% [32]. The prevalence of MAC increases nearly two-fold from approximately 35% in 65-74 year olds to nearly 60% by age ≥85 years.

In the FHS, mitral annular calcification was defined as the presence of an echo-dense band located immediately behind the posterior mitral leaflet and was assessed using M-mode echocardiography[35]. The overall prevalence of MAC in 5,694 FHS participants was 2.8%. The prevalence of MAC, in both men and women, was found to increase with age. In contrast to individuals younger than 59 years of age, in whom the prevalence was less than 1%, males and females in the oldest age groups of ≥80 years increased to 22.4% for females and 6.0% in males. Despite differences in echocardiography detection, both epidemiologic studies detected an increase in the prevalence of MAC with advancing age.

1.1.8.2 Calcification of the Coronary Arteries

Coronary arteries may also exhibit calcification and the amount of coronary artery calcification correlates with the atherosclerotic plaque burden[36]. The amount of CAC can be quantified by non-invasive methods, including electron-beam computed tomography (EBT) and multi-detector computed tomography (MDCT), and commonly reported using the agatston scoring method[37]. As previously mentioned, CAC is useful in CVD risk prediction and adds to models incorporating traditional CVD risk factors and therefore some national guidelines have incorporated them into their risk stratification models[38]. Moreover, the prognostic utility of CAC in prediction of coronary events has been demonstrated in various races[39].

There is a strong association between CAC and age with a wide range of CAC scores in the oldest old[26] . Older adults with CAC are more likely to have prevalent subclinical and clinical CVD[40]. Given its association with prevalent CVD, CAC remains discriminatory for future CVD in older adults. In addition to the relationship with coronary events, CAC in older adults has been associated with reduced physical function[41].

1.2 ASSESSMENT OF CARDIOVASCULAR RISK

The method endorsed for the CVD risk stratification and subsequent management of all persons is based upon a global risk assessment[42,43]. The Framingham Heart Study's Global Risk Score stratifies individuals into one of three categories (low, intermediate, high) based upon a 10-year estimate of CHD risk and serves as a risk stratification tool[42]. While a 10-year risk estimate of less than 10% represents a low risk, estimates of 10% to 20% and ≥20% represent an intermediate and high risk, respectively. When this method is used for cardiovascular risk stratification in older adults, age is weighted so heavily that in many cases, treatment decisions could be made on the basis of age alone. In Cardiovascular Health Study, men over 65 and women over 75 years of age had an absolute rate of CHD morbidity and mortality exceeding 2% per year or 20% over 10 years, thus would be candidates for preventive intervention of the same level of aggressiveness as other high risk groups[6].

The measurement of subclinical CVD, in addition to age, has also been proposed as a method of risk stratification[44]. Several methods, including the coronary artery calcium score provide additional discrimination even taking into account traditional risk factors[45]. In fact, coronary artery calcium has been shown to do better than age itself as a predictor of CHD risk [46].

Conventional cardiovascular risk factors, including hypertension, hyperlipidemia, smoking, physical inactivity, diabetes mellitus are highly prevalent in individuals with cardiovascular disease[47] . Except for smoking, the prevalence of every major cardiovascular risk factors increase with age[48]. Additionally, epidemiologic studies have revealed a number of the primary risk factors for an incident myocardial infarction, such as diabetes, hypertension, dyslipidemia, and smoking, remain of prognostic significance for not only the initial but also recurrent CVD, in addition to mortality[49-53]. For instance, the presence of diabetes remains a significant predictor poor prognosis after a myocardial infarction[52]. Based on data from 1,635 participants (aged 45-70 years) of The Stockholm Heart Epidemiology Program (SHEEP), the presence of diabetes was associated with an adjusted hazard of 1.6 (95% CI: 1.0-2.4) in men and 2.5 (95% CI: 0.9-6.9) during a median follow-up of 7.2 years post-MI [54]. As for the association between dyslipidemia and recurrent CVD events, several clinical trials have revealed that lipid lowering therapy with statins results a reduced risk for recurrent events[55-57]. Of note, the findings from studies reporting on the impact of smoking status on risk of recurrent events have been mixed. Despite mix findings, it has been found that there is an elevated risk of recurrent coronary events in active smokers. Based on Health Maintenance Organization data from 2,619 survivors of myocardial infarction, the risk of recurrent coronary events was significant in active smokers (Hazard Ratio: 1.51, 95% CI: 1.10-2.07)[53]. In addition, among smokers who quit smoking after initial MI there is a decrease in risk of recurrent events with time such that by 3 years after cessation the risk approaches that of non-smokers.

Other factors including increased adiposity, a low socioeconomic status, psychosocial factors (i.e., job strain), an elevated plasminogen activator inhibitor 1, and elevated inflammatory markers, such as C-reactive protein, remain as significant risk factors for recurrent CVD events[58-62].

Conventional risk factors are associated with CVD and remain important for risk prediction in old age. Moreover, given that the magnitude of the impact from preventative measures depend on the absolute baseline risk, the higher baseline CVD risk in older adults translates into a greater absolute CVD risk reduction. However, several factors make the interpretation of the associations between risk factors and CVD in the older adults challenging. The relative risks for some cardiovascular risk factors decrease in magnitude with an increase in age while their absolute effects become greater at old age[63, 64]. This has lead to misconceptions about the importance of these risk factors in old age. Relative risk represents a ratio of risk for developing the outcome, such as CVD, in individuals having a high level of a risk factor in comparison to those with low levels. One major reason for this relative reduction in risk is that the comparison group includes many individuals whose risk factors, for example cholesterol, have declined secondary to comorbid illness, therefore reducing the apparent relative differences. The absolute risk of CVD associated with risk factors continue to increase with age and most trials of risk factor reduction show marked decreases in absolute risk, with a much smaller number needed to treat.

1.3 PREVENTION OF CARDIOVASCULAR DISEASE

The approach to CVD prevention is in large part similar across all ages. The combination of pharmacologic therapy, including anti-platelet, anti-hypertensive and lipid lowering medications, along with therapeutic lifestyle changes (TLC) including physical activity may be appropriate based on individual risk. Evidence from clinical trials supports the role of TLC in achieving a favorable risk factor profile. The favorable impact of physical activity of the traditional risk factors are discussed later in this review.

1.3.1 Anti-Hypertensive Therapy in Older Adults

Hypertension is highly prevalent in the U.S. with an estimated 42.7 million adults being identified as hypertensive according to data from the Third National Health and Nutritional Examination Survey (NHANES III)[65]. Hypertension is also highly prevalent in old age, present in nearly two-thirds of individual aged ≥ 65 years. According to NHANES III data, the prevalence of hypertension increases from 3.4-8.6% in individuals aged 20-34 years, to 42.9-44.2% in persons aged 55-64 years, and increases to 64.2-77.3% in individuals aged ≥75 years[66]. In addition to being commonly present in older adults, hypertension in the elderly remains a risk factor for coronary events, strokes, and peripheral arterial disease increasing the relative risk of their occurrence nearly 1.5-2.5 fold[67-70].

Several major clinical trials have been conducted specifically in older adults and have demonstrated that blood pressure control is critical to prevention of heart disease, stroke, and mortality in older adults (TABLE 1.1)[56, 71-76]. Prior to availability of the results from the Hypertension in the Very Elderly Trial (HYVET), trials of antihypertensive therapy had established the beneficial effects of blood pressure lowering on CVD outcomes, including strokes and other vascular events, in adults up to approximately 80 years of age. These major randomized trials in older adults have clarified the role of antihypertensive therapy for prevention of CVD events in older adults (ages up to approximately 80 years) with either isolated systolic hypertension[56, 76] or an elevation of both systolic and diastolic blood pressure[71, 74]. However, given the existing evidence for an inverse relationship between blood pressure and the risk of death among individuals 80 years of age and older it had remained unclear whether the benefits of anti-hypertensive therapy could be extrapolated to adults aged ≥ 80 years[77-79]. Two studies, a subgroup meta-analysis of randomized control trials of anti-hypertensive drugs in the elderly and a randomized placebo controlled trial, investigated the role of anti-hypertensive therapy in the subpopulation of elderly aged ≥80 years[73, 75]. The subgroup meta-analysis of a total of 1,670 adults aged ≥80 years suggested that anti-hypertensive therapy in this subpopulation results in a 34% reduction in strokes, 22% reduction CVD events, and 39% reduction in heart failure. However, relationship between antihypertensive therapy and mortality in persons aged ≥80 years remained unanswered until the results of HYVET became available. The HYVET trial, which was a randomized placebo controlled trial of 3,845 adults aged ≥80 years (mean age, 83.6 years), used a diuretic-based anti-hypertensive treatment regimen to achieve the target blood pressure (BP) of 150/80 mm Hg[73]. After a median follow-up duration of 1.8 years, anti-hypertensive therapy resulted in a significant 30% reduction in strokes and 64%

reduction in heart failure. Additionally, there was a significant 21% reduction in all-cause mortality in the treatment arm relative to placebo. In summary, treatment of hypertension in the elderly is beneficial in preventing strokes, heart failure, and mortality.

Questions do remain about what should be used as the appropriate target blood pressure (BP) for older adults. The target BP used in existing trials regarding BP lowering in hypertensive elderly (ie, 150/80 mm Hg in HYVET) are different from published guidelines[80]. Current approaches should take this into account when translating these guidelines to older adults. While keeping to the published BP targets, the clinicians should be aware of the major benefit achieved in studies of older adults that have lower blood pressure by 25 mmHg or to less that 150/90 mm Hg.

Additional outcomes where the data regarding the use of anti-hypertensive therapy are not yet definitive relates to the effects on cognitive decline and dementia. Anti-hypertensive therapy may maintain cognitive functioning by reducing the progression of cognitive impairment and the reduction of incident dementia[81, 82]. The vascular dementia project, which was part of the Syst-Eur trial, aimed at comparing antihypertensive treatment with placebo in 2,418 adults aged ≥60 years (mean age, 69.9 years) in terms of their association with the risk of incident dementia. In this study, an incident dementia was initially detected based on a Mini-Mental State Exam (MMSE) and confirmed in participants with an MMSE score of 23 or less using the criteria set by the Diagnostic and Statistical Manual of Mental Disorders, revised (DSM-III-R). Following a median duration of 2.0 years, anti-hypertensive therapy with Nitrendipine, a calcium channel blocker, alone or in combination with an Angiotensin Converting Enzyme Inhibitor (ACEI) or a Thiazide diuretic resulted in a 50% relative reduction in incident dementia. Although a report by SHEP investigators failed to find a significant association between diuretic-based anti-hypertensive therapy with Chlortalidone, follow-up analysis raised the possibility this finding may have been biased by differential dropout[81, 83].

Another topic of importance in approaching CVD risk reduction in older adults is the choice of anti-hypertensive medication. The Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), which provided guidance on this issue, was a randomized active-controlled trial of 33,357 hypertensive adults with 1 additional CVD risk factor comparing four classes of antihypertensive agents[84]. The study population included 24,330 individuals aged ≥55 years. The primary outcome of ALLHAT was a combined fatal CHD or nonfatal MI. The secondary outcomes were all-cause mortality, stroke, combined CHD (primary outcome, coronary revascularization, or angina with hospitalization), and combined CVD (CHD, stroke, treated angina without hospitalization, heart failure, and peripheral arterial disease). The ALLHAT investigators concluded that treatment with a Thiazide diuretic is preferred as the initial-step in therapy of most patients with hypertension[85]. This is in support of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure (JNC 7) recommendations for antihypertensive therapy in the general population of hypertensive persons, including older adults[80].

1.3.2 Lipid Lowering Therapy with Statins in Older Adults

Similar to other preventive measure, the intensity of lipid lowering therapy is adjusted according to an individual's absolute CVD risk. The recommendation by the Adult Treatment Panel III (ATP III) serves as a useful guide in achieving this task[43, 86]. According to the guideline, those at high risk are individuals with known coronary heart disease or in whom the 10-year risk associated with their risk factors is estimated to be 20% or greater. Also, persons with known diabetes, metabolic syndrome, or an acute coronary syndrome, in addition to individuals with an established CVD are considered, are to be considered at very high risk. While all persons in the high risk categories should have an LDL-C goal of <100 mg/dL, the target of an LDL-C <70 mg/dL should be considered for adults at very high risk. In the case of older adults, the evidence supports the use of Statin therapy in high risk older persons with or without an established CVD.

Several studies of lipid lowering agents, the 3-hydroxy-3-mehtylglutaryl coenzyme A reductase inhibitors (Statins) in particular, have been conducted specifically in older adults or have included adequate number of older adults to support that effective and safely of lipid lowering with Statins to at least age 80. The Statins have been shown to be effective in the reduction of Low Density Lipoprotein cholesterol (LDL-C) levels, CVD morbidity, and both CVD-specific and all-cause mortality. These findings have been replicated in both studies with the goal of primary and secondary prevention of CVD. Moreover, the beneficial effects on clinical outcomes have been shown to be independent of baseline cholesterol levels.

Randomized trials have shown statins use to be efficacious for the primary prevention of CVD in high risk middle-aged adults and younger elderly (TABLE 1.2)[87-91]. Additionally, a recent meta-analysis evaluating the role of statins in the primary prevention of CVD revealed that statin use resulted in significant reductions in major cardiovascular events, myocardial infarctions, all-cause mortality, and CVD mortality supporting the beneficial role of statins in primary prevention of CVD[92].

Secondary prevention trials of statins have revealed that statins are efficacious for adults of wide age range and across a broad range of baseline cholesterol values. Several of these secondary prevention studies utilizing statins as the lipid lowering agent are displayed in TABLE 1.3[55-57]. These randomized placebo controlled trials of statins in adults with established coronary heart disease (CHD) have shown statins to be useful in reducing new events, including nonfatal MI, coronary revascularization, strokes, CHD-related mortality, and all-cause mortality. Similar to findings of the CARE and LIPID trials with participants whose cholesterol levels were considered to be of average levels, the 4S trial revealed a beneficial effect of statins in secondary prevention by reducing incident events and mortality in both the young (aged <60) and older (aged≥60) participants with elevated cholesterol and prevalent CHD.

Furthermore, based on the available data statins appear to have a favorable safety profile. Despite a concern for the association of statin use with increased cancer, meta-analyses of major statin trials have failed to replicate similar associations[90, 93, 94]. Evidence from existing trials has found the side effects related to statin use to be infrequent[95]. Moreover, there is no evidence to date to the fact that the statin safety profile would differ in the oldest old age group(ie, ages 80 years and older).

1.3.3 Aspirin Therapy in Older Adults

Aspirin, a cyclooxygenase inhibitor which leads to the blockade of platelet thromboxane A_2 formation, is an effective primary and secondary prevention measure in high risk populations. However, the incorporation of aspirin therapy requires consideration for the associated increased risk of hemorrhage, including major gastrointestinal bleeding. Based on a recent study, the estimated incidence rate (per 1,000 person-years) of aspirin associated upper gastrointestinal tract complications among men and women without any prior risk factors or use of NSAIDS increases from 4.8 and 2.4 among adults aged 60-69 years to 12.0 and 6.0 in adults aged $\geq$ 80 years[96]. The rates of gastrointestinal harm associated with aspirin use are approximately two-fold greater than non-aspirin user and one-fourth the rate associated with the combined use of aspirin with NSAIDS.

Prior guidelines recommended the use of aspirin for the primary prevention of CHD in both males and females considered to be at high risk[97,98]. Based on the evidence from more recent studies, including the results the Women's Health Study[99], the U.S. Preventive Services Task Force (USPTF) has published their new recommendations[100]. In the publication, the USPTF encourages aspirin use for the reduction of myocardial infarctions in men aged 45-79 years and ischemic strokes in women aged 55-79 years when the potential benefit outweighs the harm of an increase in gastrointestinal hemorrhage. The Task Force report provides estimates for the benefits associated with aspirin use, the number of MI's in men and the number of strokes in women, utilizing the results of a recent meta-analysis of aspirin use for primary prevention which revealed that aspirin use was associated with a 32% relative reduction in MI and a 17% relative reduction in ischemic strokes[101]. Similarly, the estimates of gastrointestinal harm were based on rates of gastrointestinal bleeding in non-NSAID taking persons who did not have upper GI pain or a history of GI ulcer[96]. The 10-year CHD risk threshold at which the benefits of aspirin use for the prevention of MI in men outweighs the potential harm increases from 4% in men aged 45-49 years to 12% in men aged 70-79 years old. Similarly in women, the 10-year CHD risk threshold at which the benefits of aspirin use for stroke prevention outweighs the potential harm increases from 3% in women aged 55-59 years to 11% in women aged 70-79 years old. However, more evidence is needed regarding the both the risks and the benefits of aspirin use in CVD prevention for older adults, especially the oldest old age group (ages 80 years and older).

1.3.4 Physical Activity and Fitness

The Center for Disease Control/American College of Sports Medicine (CDC/ACSM) physical activity guidelines recommend a minimum of 30 minutes of moderate intensity physical activity on 5 or more days per week or vigorous activity of at least 20 minutes duration on 3 more days per week[102]. In older adults, a daily walk of at least 20 to 30 minutes which is considered a moderate intensity activity would likely achieve a level of fitness resulting in significant reduction in mortality risk[103]. However, only 39% of U.S. adults aged 65 years and older meet the CDC/ACSM. Given the projected growth of the segment of the U.S. population aged 65 years and older in the future decades, prevention efforts promoting regular physical activity would lead to a substantial reduction in morbidity and mortality [42].

1.3.4.1 Prognostic significance of Physical Activity and Fitness

Physical activity or fitness has a favorable impact on the risk of mortality. For instance, the benefit anticipated if a physically unfit man or woman would become fit would be a change of 36.7% and 48.4% reduction in his or her risk of dying[104]. In order to place into perspective, a man or woman with high serum cholesterol (≥ 6.2 mmol/L) would reduce their risk by 39.3% and 40.5% if he or her lowered it, respectively[104]. In comparison, a man or woman with a high systolic blood pressure (≥ 140 mm Hg) would reduce their risk by 26.5% and 55.1% if he or her lowered it, respectively[104]. In terms of the impact at the population level, the death rates would be a 9.0% lower in men and 15.3% lower in women if an unfit individual becomes fit[104].

The favorable effect of physical activity level in reducing the risk of mortality due to premature CVD, CHD, and all-cause mortality in middle-aged adults has been observed by a number of observational studies[105-108]. As in middle-aged adults, the inverse association between physical activity and all-cause mortality has been shown in several studies of older adults[109-115]. Despite the number of studies on the inverse association between physical activity and CHD-specific mortality in middle-aged adults, the literature on this relationship in older aged adults have been equivocal. Table 1.4 displays the findings of several studies reporting on the relationship between physical activity in older adults with all-cause and CHD-specific mortality. Similarly, the summary of the findings of studies of the relationship between fitness in older adults with all-cause mortality is shown in Table 1.5.

The effect of physical activity has also been observed for leisure-time physical activity (LTPA)[116]. Regular LTPA is associated with a lower risk for all-cause and cardiovascular disease morbidity and mortality in high risk middle-age adults. A higher level of LTPA has been shown to be associated with reduced incident of coronary heart disease (CHD) and mortality[117,118]. The Multiple Risk Factor Intervention Trial(MRFIT) reported on the association between LTPA with the first coronary heart disease event. In the MRFIT study of 12,138 middle-aged men (mean age 46 years) over a mean 7 years of follow-up revealed a statistically significant 36% relative risk reduction for coronary heart disease death and sudden death endpoint and a 27% risk reduction for all-cause mortality in moderately active individuals relative to light active group. In addition, there was a favorable trend for the endpoint of nonfatal myocardial infarction when comparing the heavy versus the light physical active individuals. Regarding the association of LTPA with reinfarction, among survivors of a first MI in the Corpus Christi Heart Project (mean age of 60.2 years) those individuals who increased their LTPA had a higher reinfarction rate (17 per 1000 years) as compared to sedentary individual whose LTPA remained unchanged[119].

1.3.4.2 Relationship of Fitness with Age

Cardiorespiratory fitness or capacity declines with increasing age[120, 121]. The estimated decline with increasing in age ranges from 5.5% in trained master athletes to 12% decline in peak oxygen consumption per 10 year in sedentary adult men[120]. While the rate is attenuated after accounting for muscle mass, this age-related decline in cardiorespiratory fitness is persists in both men and women[122, 123]. In addition to age and gender, several other factors are have been associated with cardiorespiratory fitness including the duration, intensity, frequency, and type of physical activity, cardiovascular risk factors, clinical and subclinical disease, medications, and genetic factors[124]. It has been estimated that genetic factors account from 25% to 40% of cardiorespiratory fitness[125].

1.3.4.3 Effects of Physical Activity on Cardiovascular Risk Factors

The favorable effect of physical activity on CVD risk reduction is likely mediated via a combined favorable effect on traditional cardiovascular risk factors, non-traditional factors, and other unknown factors[125]. Most physically active individual will have a change in the order of magnitude between 2% to 5% in their traditional cardiovascular risk factors, including 5% decrease in lipids[126], 3 to 5 mm Hg lowering of blood pressure[127], and a 1% lowering of HgbA1c[128]. Additionally, regular physical activity result is reductions in inflammatory markers[128], including C-Reactive Protein[129, 130].

1.3.4.4 Assessment of Physical Fitness

Cardiorespiratory or physical fitness is condition which is measured more objectively than the behavior of physical activity. Physical activity is a behavior which is modifiable and that serves as a determinant of physical fitness[104]. While fitness may serve as a marker of physical activity level, the objective measurement of fitness is more precise than the self-reported physical activity typically captured via questionnaires[131]. While studies have between consistent with respect to the direction of association between fitness or activity and health outcomes, the objective measurement of fitness likely accounts for the greater strength of association between fitness and outcomes.

Fitness can either be measured by an exercise treadmill or cycle ergometer testing or walk-based tests. The oxygen uptake (VO2), either peak or maximal, is a product of the cardiac output and arteriovenous oxygen difference is obtained from exercise testing. The oxygen uptake can also be reported in metabolic equivalents (METs), where one MET is equivalent to oxygen uptake of 3.5 mL/ kg per min. The MET represents a ratio of the metabolic rate during exercise to the resting metabolic rate. The oxygen uptake can either be directly measured or can also be estimated via established normograms with the direct measurement representing the gold standard[132]. Several factors contribute to the discrepancy seen between directly measured versus estimated oxygen uptake including the level of familiarity with the treadmill protocol, use of handrail support, submaximal versus maximal testing, and population differences[124].

Oxygen uptake is conventionally obtained according to either a maximal or sub-maximal treadmill-based protocols or cycle ergometry exercise testing. Treadmill-based and walk-based testing represent alternate methods for the assessment of functional exercise capacity[124]. While the treadmill exercise test has been the most commonly applied method for the assessment of exercise capacity, older adults encounter greater limitations in their ability to execute a treadmill based exercise test[133]. Moreover, the submaximal performance during a walking test in older adults may be a better reflection of daily activities and a more practical method of assessment than treadmill-based protocols[134-136].

Six Minute Walk Test

The 6 MWT was introduced after 1976 with the use of the 12-minute corridor walking test[137]. The 6 MWT is a simple, safe, and easily administered test which has been studied in various disease specific populations, such as those with pulmonary disease, heart failure, pacemakers, peripheral arterial disease, and organ transplant candidates[138-144]. In older adult populations the 6 MWT is a reliable and valid measure of functional capacity[145]. The distance walked during six minutes has been shown to be an independent predictor of morbidity and mortality in various disease-specific populations as displayed in Table 1.6.

1.4 TABLES FOR INTRODUCTION

Table 1.1 Studies of Anti-Hypertensive Therapy in Older Adults

Study	Population	Treatment	Follow-up	Summary
SHEP[72]	n=4,736; Age: 72yr, mean	Diuretic (Chlorthalidone) or Placebo	Mean:4.5yr	A Significant 36% reduction in stroke, 54% in left ventricular failure, and a 33% reduction in myocardial infarction. No significant reduction in CVD-related or all-cause mortality.
MRC[71]	n=4,396; Age:70yr, mean	Diuretic (Chlorothiazide or Amiloride) or β-blocker (Atenolol) or Placebo	Mean:5.8yr	A significant 31% reduction in risk of stroke, 44% reduction for coronary heart disease, 35% reduction in cardiovascular events, and 29% reduction in cardiovascular deaths in the diuretic arm.
STOP-Hypertension[74]	n=1,627; Age:76yr, mean	Diuretic and/or β-blocker or Placebo	Mean:25mo	A significant 47% relative reduction in all type stroke, and 43% reduction in all-cause mortality.
Syst-Eur[76]	n=4,695; Age:70yr, mean	Calcium Channel Blocker, Angiotensin Converting Enzyme Inhibitor, and/or Hydrochlorathiazide or Placebo	Median:2yr	A significant 42% reduction in stroke (fatal and non-fatal), and 26% reduction in fatal and non-fatal cardiac endpoints (heart failure, myocardial infarction, and sudden death) rates.

Abbreviations: SHEP refers to Systolic Hypertension in the Elderly; MRC, Medical Research Council trial; STOP-Hypertension, Swedish Trial in Old Patients with Hypertension; Syst-Eur, Systolic Hypertension in Europe trial; n, sample size; yr, year; mo, months.

Table 1.2 Studies of Lipid Lowering Therapy with Statins for Primary Prevention

Study	Population	Treatment	Follow-up	Summary of Results
WOSCOPS[91]	6,595 with hypercholesterolemia Age: range, 45-64 yr	Pravastatin 40 mg/d or Placebo	Mean: 4.9 yr	31% reduction in non-fatal MI or CHD mortality; 22% reduction in total mortality
AFCAPS/TexCAPS[88]	6,605 with average cholesterol levels (LDL-C mean, 150 mg/dL) Age: mean,58 yr; Range, 45-73 yr; Included 1,416 persons aged ≥65 yr	Lovastatin 20-40 mg/d or Placebo	Mean:5.2 yr	37% reduction in fatal or non-fatal MI, unstable angina, or sudden death, 40% reduction in fatal and non-fatal MI, 25% reduction in total CV events, 25% reduction in fatal and non-fatal coronary events, and 33% reduction in revascularizations.
HPS[87]	20,536 at high risk Age: range, 40-80 yr; Included 5,806 persons aged ≥70 yr	Simvastatin 40 mg/d or Placebo	Mean: 5 yr	Approximately 25% reduction in rate of non-fatal MI or coronary death, fatal or non-fatal stroke, and coronary or non-coronary revascularization
ASCOT-LLA[89]	10,305 with hypertension Age: mean, 63 yr; range, 40-79 yr; Included 6,570 persons aged ≥60 yr	Atorvastatin 10 mg/d or Placebo	Median: 3.3 yr	36% reduction in endpoint of non-fatal MI, including silent MI, and fatal CHD.
PROSPER[90]	4,695 participants Age: mean, 75 yr; range,70-82 yr	Pravastatin 40 mg/d or Placebo	Mean: 3.2 yr	15% reduction in endpoint of coronary death, non-fatal MI, and fatal or non-fatal stroke. Also, a 24% reduction in CHD mortality. No significant effect on rate of stroke, cognitive decline, or disability.

Abbreviations: WOSCOPS refers to West of Scotland Coronary Prevention Study; AFCAPS/TexCAPS, Air Force/Texas Coronary Atherosclerosis Prevention Study; HPS, Heart Protection Study; PROSPER, Pravastatin in elderly at risk of vascular disease; ASCOT-LLA, Anglo-Scandanavian Cardiac Outcomes Trial-Lipid Lowering Arm;. With kind permission from Springer Science Business Media: Current Cardiovascular Risk Reports, Evolving Concepts of Cardiovascular Disease Prevention in Older Adults, 3, 2009, 363-377, Yazdanyar A Newman AB, Copyright 2009.

Table 1.3 Studies of Lipid Lowering Therapy with Statins for Secondary Prevention

Study	Population	Treatment	Follow-up	Summary of Results
4S[55]	4,444 participants with hypercholesterolemia Age: mean, 58 yr (men), 61 yr (women); range, 35-74 yr; Included 2,284 persons ≥60 yr	Simvastatin 10-40 mg/d or Placebo	Median:5.4yr	42% relative reduction in coronary-related mortality, 35% reduction in all-CVD-related mortality, and 30% reduction in all-cause mortality. Also, a 37% relative reduction in non-fatal MI. Similar beneficial treatment effect in persons aged ≥60 and ≤60 years old.
CARE[57]	4,159 participants Age: mean: 59 yr; range, 21-75 yr; Included 2,129 persons aged ≥60 yr	Pravastatin 40 mg/d or Placebo	Median: 5 yr	24% relative reduction in primary endpoint of fatal CHD or MI.
LIPID[56]	9,014 participants at high risk Age: median, 62 yr; range, 31-75 yr; Included 2,168 persons aged 65-69 yr and 1,346 aged ≥70 yr	Pravastatin 40 mg/d or Placebo	Mean: 6.1 yr	A 24% reduction in CHD mortality and 22% reduction in all-cause mortality. Also, reductions in non-fatal MI and stroke.

Abbreviations: 4S refers to Scandinavian Simvastatin Survival Study; CARE, Cholesterol and Recurrent Events trial; LIPID, Long-term Intervention with Pravastatin in Ischemia; mg/d, milligrams per day; yr, year.

Table 1.4 Relationship of Physical Activity in Older Adults with Coronary Heart Disease and Mortality

Study	Study Design	Study Population	Activity Assessment	Results
Kaplan et al.[109]	Retrospective Cohort	4,174 adults aged 55 years and older (21% aged 65-70 years) residents of Alameda County, California participating in the Alameda County Study; follow-up period of 17 years	Questionnaire of seven behavioral risk factors including engaging in regular physical activity	Adults aged 60 years or more reporting low compared to high physical activity level had a higher risk of all-cause mortality (HR, 1.38; 95% CI, 1.17-1.62).
Simonsick et al.[112]	Retrospective Cohort	A total of 1,874 East Boston, 1488 New Haven, and 1,815 Iowa older adult (aged 65 years and older) participants of the Established Populations for Epidemiologic Studies of the Elderly; Outcomes assessed after 3 and 6 years of follow-up	Questionnaire of recreational physical activity such as walking.	Frequent walking was associated with reduced risk of mortality over 3 and 6 years; moderate to high activity reduced risk of physical limitation over 3 years; No significant relationship of activity with incident angina, myocardial infarction, or stroke.
Bijnen et al. [115]	Retrospective Cohort	A total of 802 older aged 64 years or more (mean, 71.4±5.2 years) Dutch men participating in the Zutphen Elderly Study; Outcomes assessed after 10 years of follow-up	Questionnaire of leisure-time physical activity.	Relative to lowest physical activity, adults in highest tertile had a reduced risk of all-cause mortality(HR , 0.77; 95% CI, 0.59-1.00) and CVD mortality (HR, 0.70; 95% CI, 0.48-1.01) but not CHD mortality (HR, 0.85; 95% CI, 0.51-1.44)
Yates et al.[114]	Prospective Cohort	A total of 2,357 older aged men (mean age, 72 years) participating in the Physicians' Health Study	Questionnaire of the frequency of vigorous exercise	Regular exercise was associated with a lower risk of mortality (HR, 0.72; 95% CI, 0.62-0.83)
Stessman et al.[113]	Prospective Cohort	A total of 1,861 aged 70 years or more participating in the Jerusalem Longitudinal Cohort Study	Questionnaire of the regular physical activity	Both Maintaining physical activity and initiating physical activity after age of 70 years were associated with reduced risk of mortality.
Abbreviations: HR represents hazards ratio; 95% C.I., 95% Confidence Interval.				

Table 1.5 Relationship of Treadmill and Cycle Ergometry Exercise-Based Fitness with Mortality

Study	Study Design	Study Population	Fitness Test	Results
Blair et al.[104]	Prospective Cohort	10,224 middle-aged men and 3120 women with a preventative medical examination at the Cooper Clinic	Maximal exercise treadmill test	Lower risk of all-cause mortality primarily due to CVD and cancer deaths with higher fitness in men and women. RR for 2 least-fit quintiles(Q) relative to most fit quintile in men were Q1 1.8(95% CI,1.4-2.4) and Q2 1.3(95% CI,1.0-1.8). In women, the risk in least fit quintile was 3.9(95% CI,1.4-11.0) relative to most fit quintile. Decline observed in death rates with higher fitness was more pronounced in older aged (>60 years).
Laukkanen et al.[146]	Retrospective Cohort	1,294 randomly selected sample of middle-aged men without prevalent cardiovascular disease in eastern Finland (mean age, 52.1 years) participating in the Kuopio Ischaemic Heart Disease Risk Factor Study	Symptom-limited bicycle ergometry test	Both exercise duration and oxygen uptake were predictors of mortality. Relative to MET>10.6, MET<7.9 was associated with HR 3.85 (95% CI, 2.0-7.3) of overall death, 3.97(95% CI,1.3-12.0) CVD-specific death, and 3.79(95% CI,1.7-8.4) non-CVD deaths. Relative to exercise duration>11.2 min, duration<8.2 was associated with HR 3.94 (95% CI, 2.0-7.7) of overall death, 4.54(95% CI,1.5-14.0) CVD-specific death, and 3.68(95% CI,1.6-8.6) non-CVD deaths.
Abbreviations: RR represents relative risk; 95% CI, 95% Confidence Interval; MET, Metabolic Equivalent.				

Table 1.5 (Continued)

Study	Study Design	Study Population	Fitness Test	Results
Goraya et al.[147]	Retrospective Cohort	514 older adults aged 65 years and older and 2,593 adults aged younger than 65 years participating in the Rochester Epidemiology Project; 48% women in elderly subgroup	Treadmill exercise test using standard Bruce, modified Bruce, Naughton protocols	In older adults, an increase of 1 MET associated with 18% decrease risk of cardiac events and 18% decreased risk of death; Mortality rate 37% in older and 8% among younger persons ($p<0.001$)
Spin et al.[148]	Retrospective Cohort	1,185 older male adults aged 65 years and older and 2,789 adults aged 65 years referred for exercise testing	Treadmill exercise test according to United States Air Force School of Aerospace Medicine or individualized ramp protocols	In older and younger subgroups, an increase of 1 MET was associated with 11% decrease risk of death; Mortality rate 23% in older and 10% among younger persons
Myers et al.[149]	Retrospective Cohort	6,213 men referred for exercise testing; age 59 +/- 11 years	Treadmill exercise test according standardized graded or individualized ramp protocols	An increase of 1 MET associated with 12% decrease risk of death; Annual average mortality rate of 2.6%
Gulati et al.[150]	Retrospective Cohort	5,721 asymptomatic women participating in the St James Women Take Heart Project; age 52 +/- 11	Treadmill exercise test according the Bruce protocol	An increase of 1 MET associated with 17% decrease risk of death; overall mortality rate was 3.2%
Messinger-Rapport et al.[151]	Prospective Cohort	6,022 adults aged 65 to 74 and 1,332 aged 75 years and older referred for exercise testing; 32% women	Treadmill exercise test according Bruce, modified Bruce, or Cornell protocol	Impaired peak exercise workload in lowest quintile for age- and sex-strata (HR, 2.1; 95% CI, 1.8 - 2.4) and impaired heart rate recovery (HR, 1.5;95% CI, 1.3 - 1.7) were associated with increased mortality risk
Abbreviations: HR represents hazards ratio; 95% CI, 95% Confidence Interval; MET, Metabolic Equivalents.				

Table 1.5 (Continued)

Study	Study Design	Study Population	Fitness Test	Results
Mora et al.[152]	Retrospective Cohort	2,994 women without cardiovascular disease participating in the Lipid Research Clinic Prevalence Study; 30 to 80 years age range	Treadmill exercise test according to Bruce protocol	A decrease in MET was associated with increased risk of all-cause (HR, 1.11; 95% CI , 1.06 - 1.17) and cardiovascular death (HR, 1.17; 95% CI, 1.07 - 1.27); A 10 beat per minute decrement in heart rate recovery was associated with an increase risk of all-cause death (HR, 1.20; 95% CI , 1.04 - 1.38)
Sui et al.[153]	Retrospective Cohort	2,087 men and 516 women participating in the Aerobics Center Longitudinal Study; age 64 +/- 5 years	Treadmill exercise test according to a modified Balke protocol	Relative to referent lowest quintile of treadmill duration, decreased risk of mortality across longer treadmill time quintiles, HR, 0.53; 0.44, 0.43, 0.30, respectively; Both fitness and BMI are independent predictors of mortality
Kokkinos et al.[154]	Retrospective Cohort	5,314 male veterans aged 65 years or more (mean age, 71.4 years; 3,224 White ad 2,090 Black) with either routine evaluation or an evaluation for exercise-induced ischemia; median follow-up of 8.1 years	Treadmill exercise test according to either a Balke protocol or an individualized ramp protocol	Compared to persons with fitness at 4 METs or less, there was reduces risk of mortality persons achieving METs 5.1-6.0 with (HR, 0.62; 95% CI, 0.54-0.71) and those achieving METs of 9 or more with HR 0.39 (95% CI, 0.32-0.49).
Abbreviations: HR represents hazards ratio; 95% CI, 95% Confidence Interval; MET, Metabolic Equivalents.				

Table 1.6 Relationship between the 6 Minute Walk Test Performance with Mortality

Study	Study Design	Study Population	Fitness Test	Results
Cahalin et al.[155]	Prospective	45 adults referred for heart transplantation evaluation; age 49 +/- 8 years	6 MWT and Cycle ergometry testing with radionuclide angiography	6 MWT distance less than 300 meters was associated with short-term (6 months) death or hospitalization for inotropic or mechanical support (p=0.04) but not long-term (p=0.14)
Bittner et al.[139]	Cross-sectional	Stratified random sample of 898 patients with ejection fraction 0.45 or less enrolled in the randomized clinical trial (SOLVD); age 59 +/- 12 years	6 MWT	Decrement of 120 meters was associated with increased mortality in heart failure with ejection fraction less than 0.45 (OR, 1.50; 95% CI, 1.11 - 2.03) and also among preserved ejection fraction (OR, 2.62; 95% CI, 1.57 - 4.37)
Rostagno et al. [156]	Prospective	214 patients either referred or admitted via emergency department for mild to moderate heart failure; age 64 years	6 MWT and treadmill exercise testing according to modified Bruce protocol	6 MWT distance less than 300 meters was associated with a higher risk of mortality (p=0.012) compared to higher distance walked; Multivariable association revealed a reduced risk of death per meter increase in walk distance (HR, 0.995; 95% CI, 0.993 - 0.997)
Shah et al.[157]	Prospective	440 symptomatic heart failure with ejection fraction 0.25 or less patients participating in a randomized clinical trial (FIRST) comparing epoprostenol and standard therapy with standard therapy alone; age 64 years in able to walk and 67 years in unable to walk	6 MWT	Decrement of 100 meters during 6 MWT distance was associated with increased risk of mortality (HR, 0.58; 95% CI, 0.50 - 0.68) and hospitalization (HR, 0.85; 95% CI, 0.46 - 0.90)
Abbreviations: 6 MWT represents 6 Minute Walk Test; HR, hazards ratio; OR, Odds Ratio; 95% CI, 95% Confidence Interval; MET, Metabolic Equivalents.				

Table 1.6 (Continued)

Author	Study Design	Study Population	Fitness Test	Results
Lederer et al.[145]	Retrospective cohort	454 patient with Idiopathic Pulmonary Fibrosis listed for lung transplantation with United Network for Organ Sharing; age 56 +/- 9 years	6 MWT	6 MWT distance less than 207 meters relative to greater distance was associated with increased waiting-list mortality risk (HR, 4.7; 95% CI, 2.5 - 8.9)
Castel et al.[158]	Retrospective cohort	188 patients with moderate to severe heart failure referred for cardiac resynchronization therapy; age 69 +/- 8 years	6 MWT	6 MWT distance less than 225 meters was associated with increased risk of mortality relative to a distance of 400 meters or longer (HR, 5.6; 95% CI, 1.2 - 25.3)
Alahdab et al.[159]	Prospective	198 African American patients with acute decompensated heart failure admitted to a single tertiary hospital; age 56 +/- 13 years	6 MWT	6 MWT distance less than 200 meters was associated with increased risk of mortality (HR, 2.1; 95% CI, 1.2 - 3.8) relative a distance 200 meters or more.
Enfield et al. [160]	Retrospective cohort	815 patients with severe Chronic Obstructive Pulmonary Disease with inpatient pulmonary rehabilitation; age 73 +/- 9	6 MWT	Post-pulmonary rehabilitation 6 MWT distance was associated with survival (HR, 1.3; 95% CI, 1.2 - 1.4)
Carey et al.[161]	Prospective	121 patients with end stage liver disease listed for liver transplantation at a tertiary medical center; age 56 +/- 9 years	6 MWT	Increase of 100 meters on 6 MWT distance was associated with lower mortality risk (HR, 0.6; 95% CI, 0.4 - 0.9)
Boxer et al.[162]	Prospective	60 patients recruited from a heart failure clinic; age 78 +/- 12 years	6 MWT	Increase of 30 meters during 6 MWT distance was associated with decreased risk of mortality (HR, 0.82; 95% CI 0.72 - 0.94) along with an increase risk associated with markers of frailty (HR, 1.64; 95% CI, 1.19 - 2.26)
Abbreviations: HR represents hazards ratio; OR, Odds Ratio; 95% CI, 95% Confidence Interval; MET, Metabolic Equivalents; 6 MWT, 6 Minute Walk Test.				

1.5 FIGURES FOR INTRODUCTION

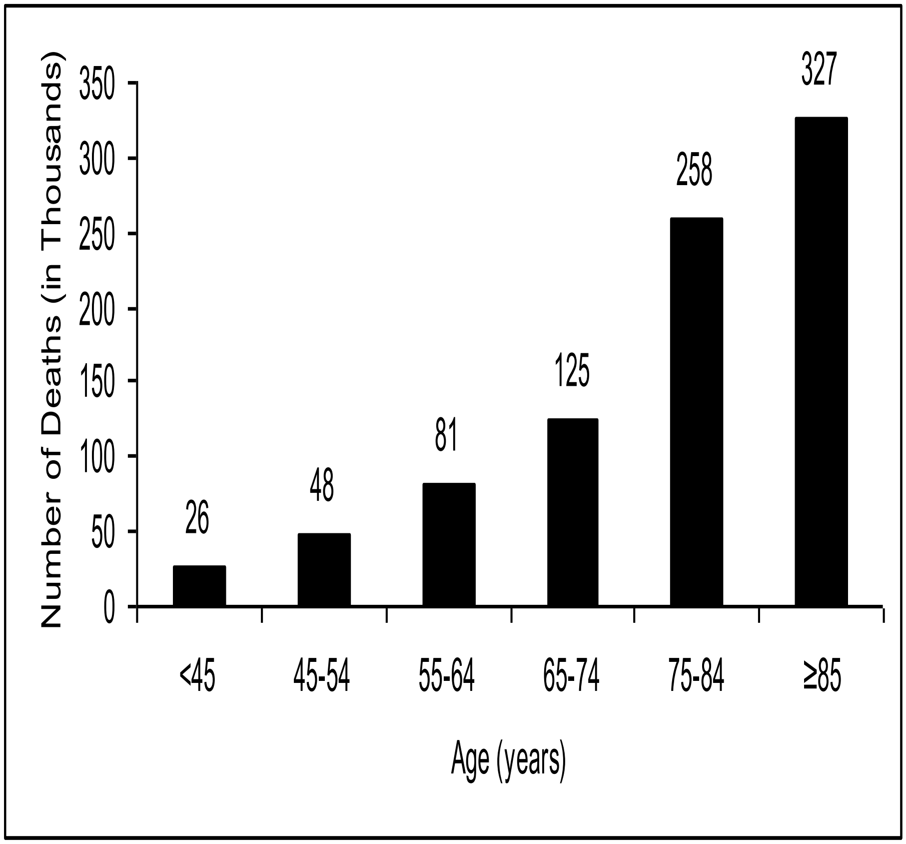

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Figure 1.1 Number of Deaths (in thousands) due to Cardiovascular Diseases by Age in 2005

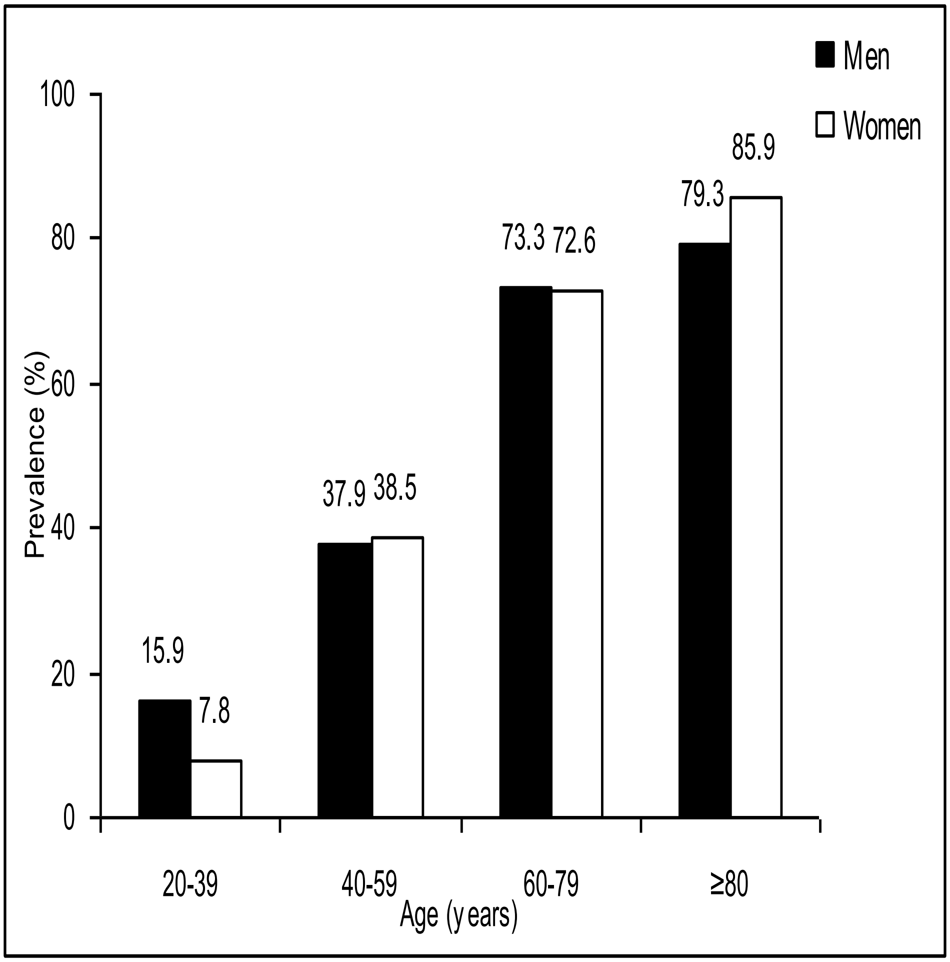

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Figure 1.2 Prevalence of Cardiovascular Disease in Adults aged 20 Years and Older by Age and Sex

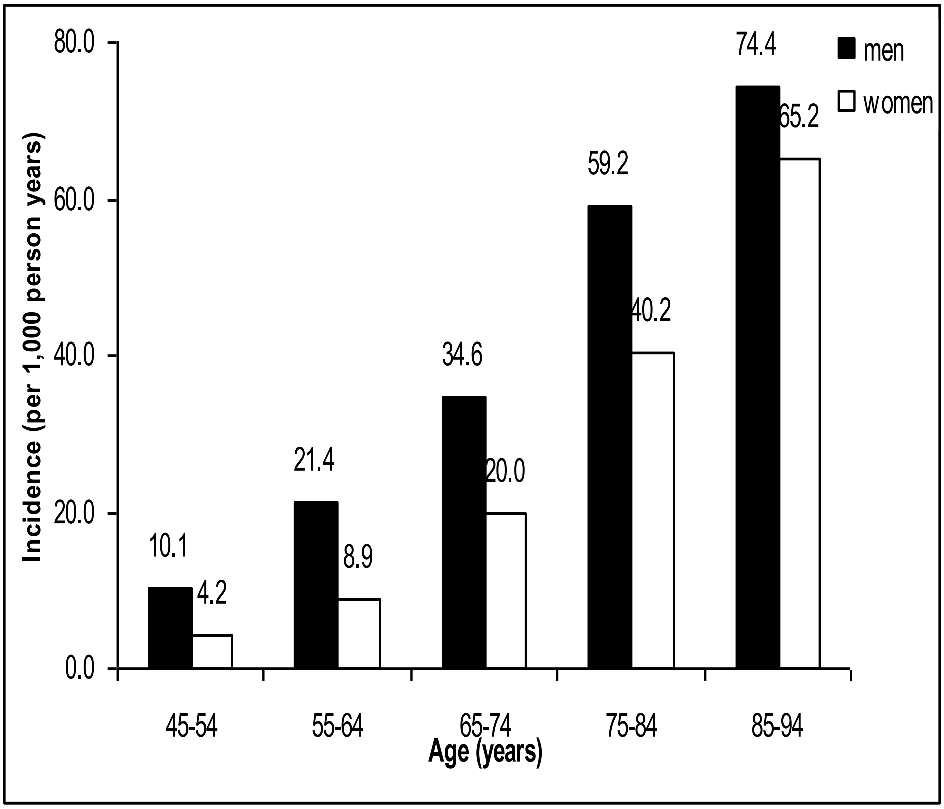

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Figure 1.3 Incidence of Cardiovascular Disease in Adults Aged 45 Years and Older by Age and Sex

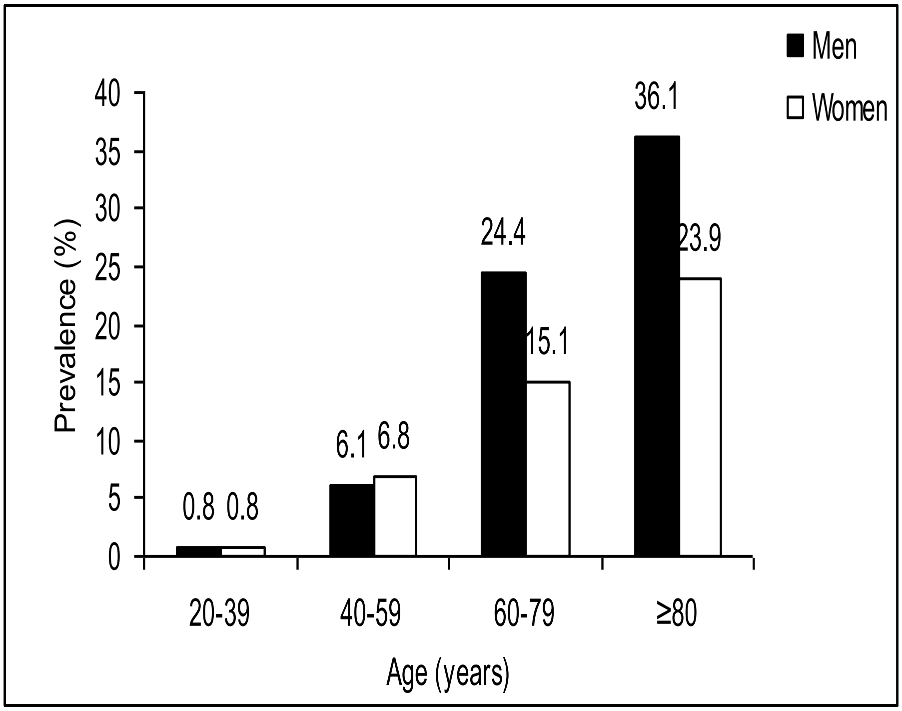

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Figure 1.4 Prevalence of Coronary Heart Disease in Adults Aged 20 Years and Older by Age and Sex

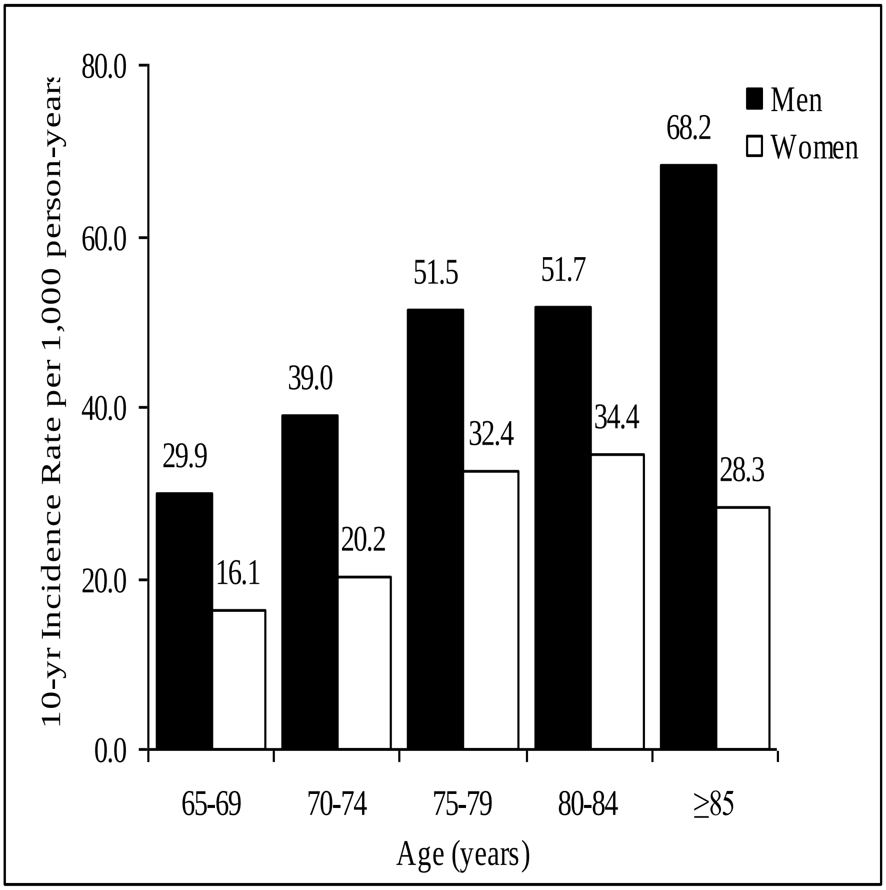

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Figure 1.5 Ten Year Incidence Rate of Coronary Heart Disease in Caucasians by Age and Sex: Cardiovascular Health Study

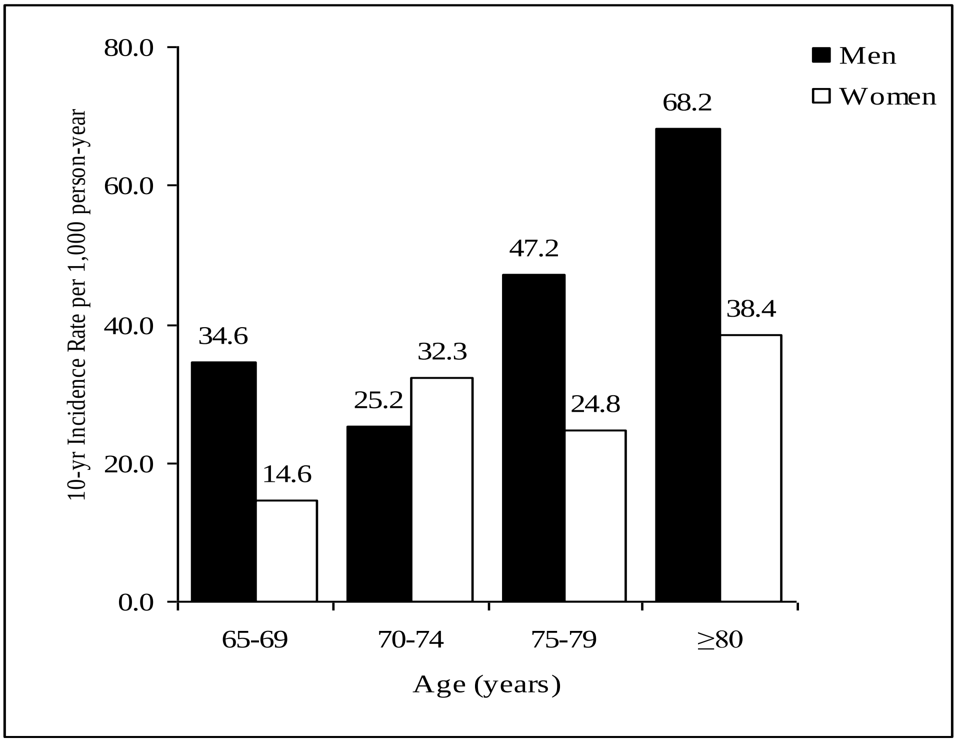

Figure 1.6 Incidence Rate of Coronary Heart Disease in African Americans by Age and Sex: Cardiovascular Health Study

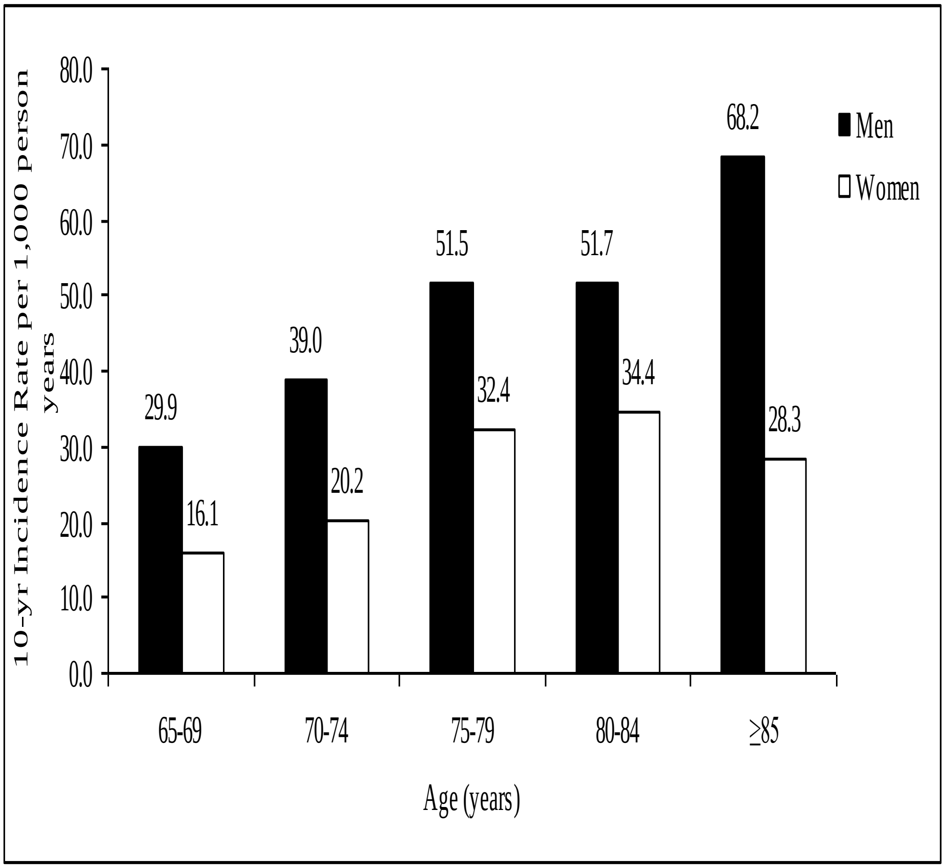

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Figure 1.7 Ten Year Incidence Rate of Myocardial Infarction in Causasians by Age and Sex: Cardiovascular Health Study

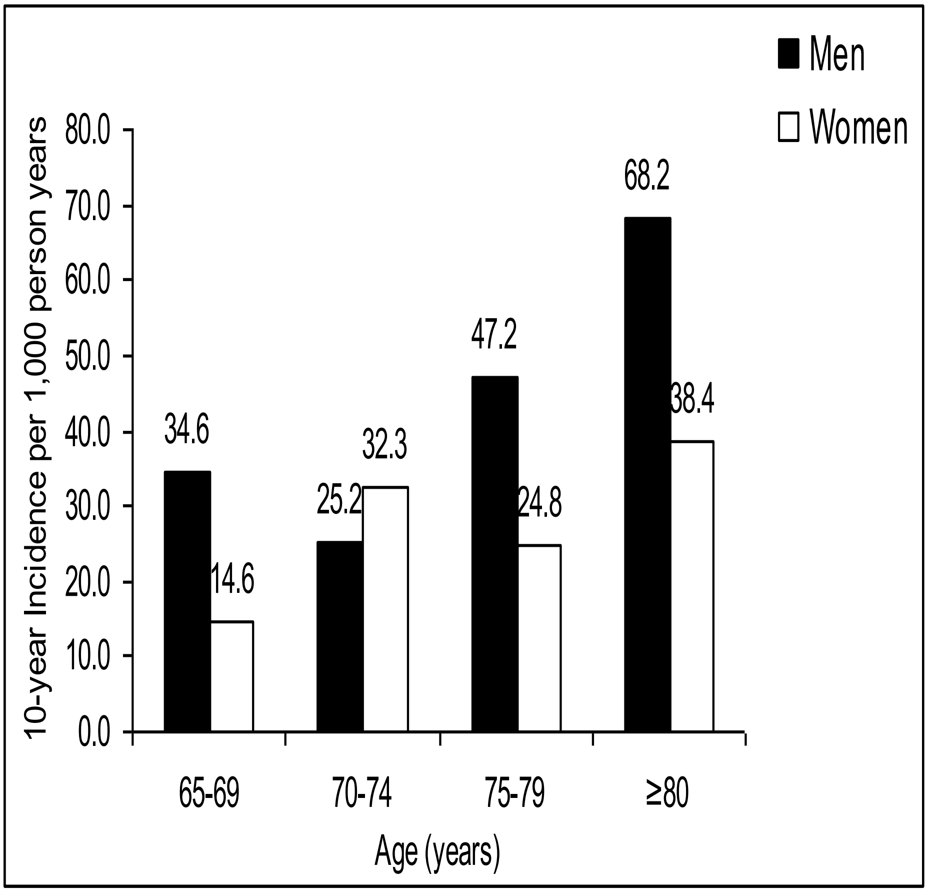

Figure 1.8 Ten Year Incidence of Myocardial Infarction in African Americans by Age and Sex: Cardiovascular Health Study

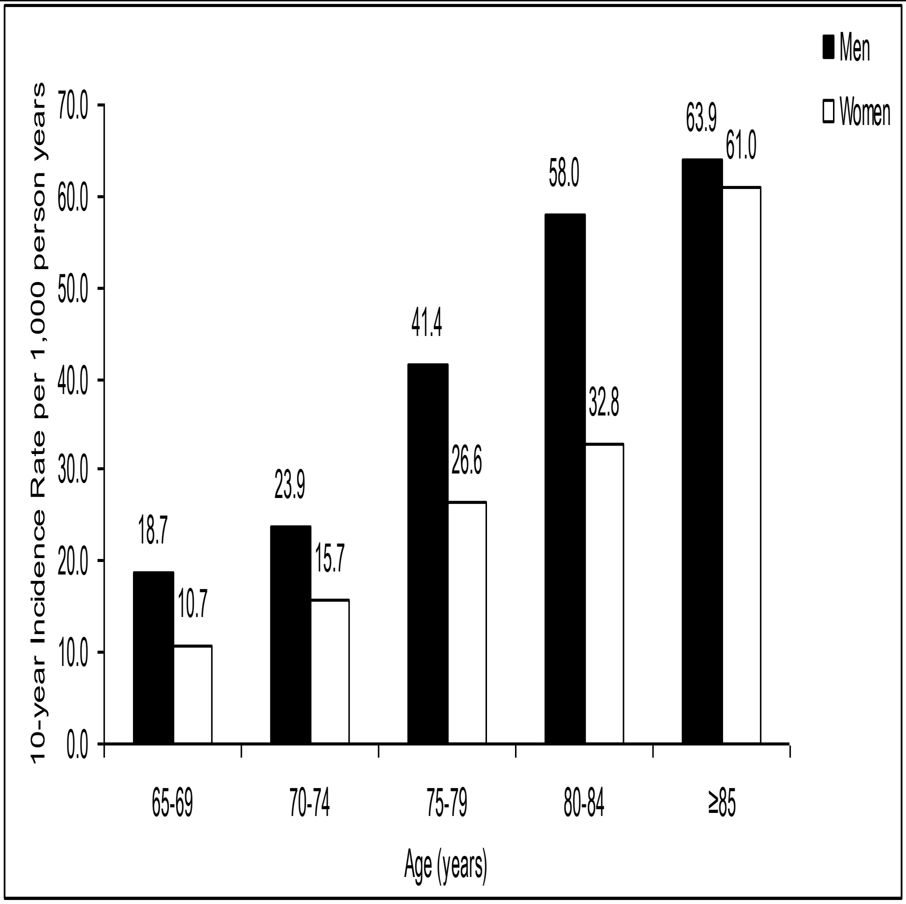

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Figure 1.9 Ten Year Incidence of Heart Failure in Caucasians by Age and Sex: Cardiovascular Health Study

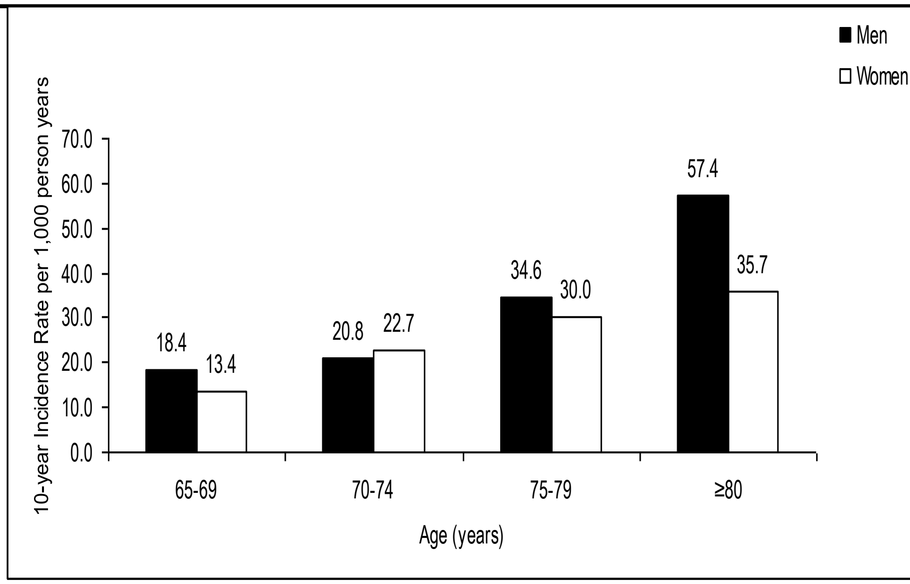

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Figure 1.10 Ten Year Incidence of Heart Failure in African Americans by Age and Sex: Cardiovascular Health Study

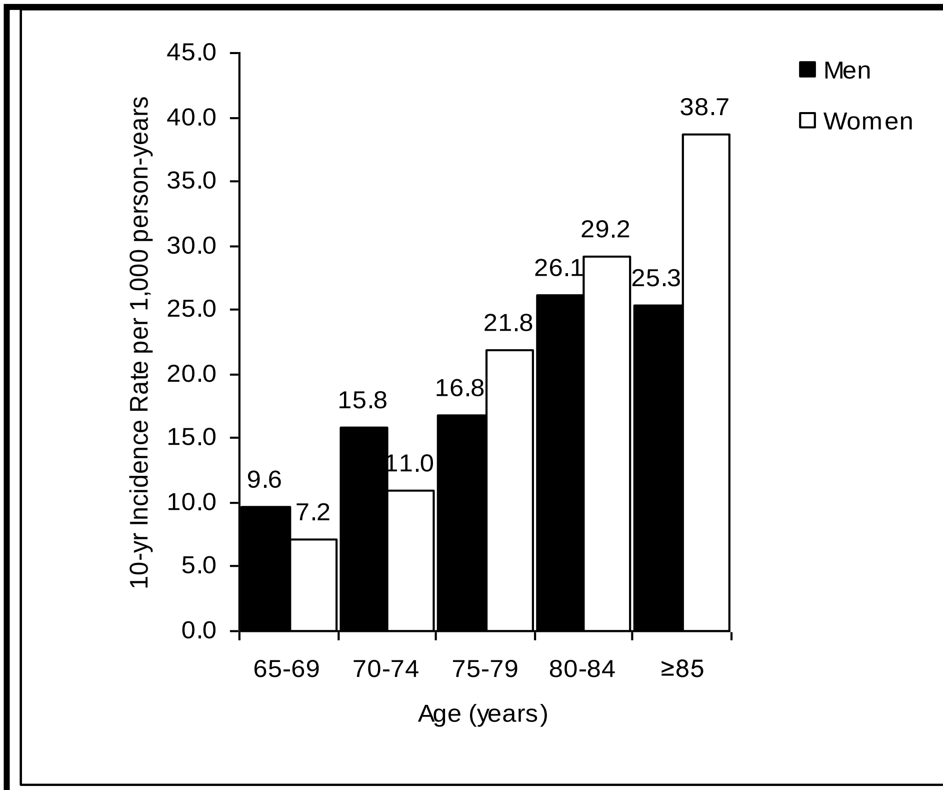

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Figure 1.11 Ten Year Incidence of Stroke in Caucasians by Age and Gender: Cardiovascular Health Study

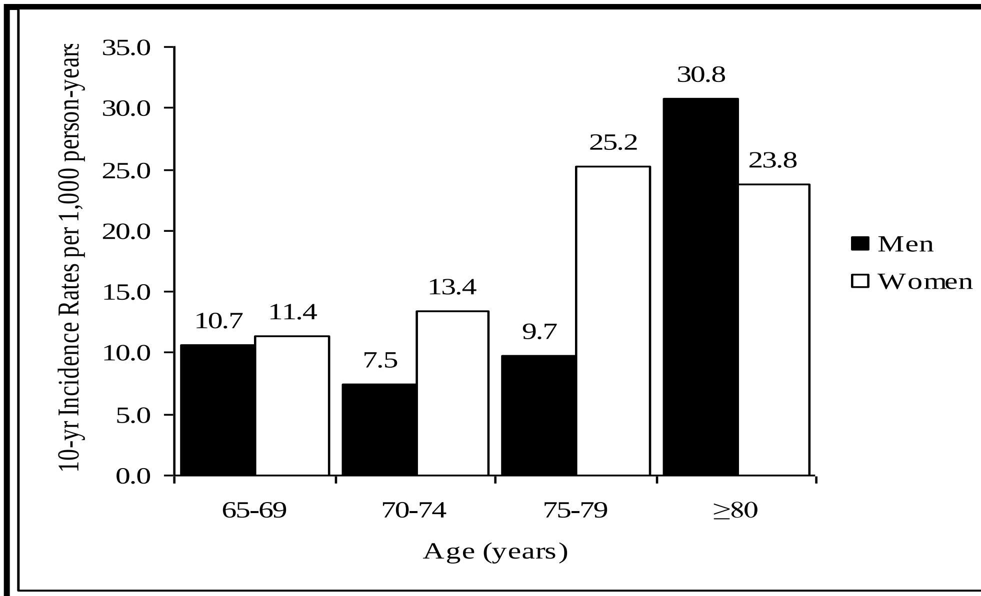

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Figure 1.12 Ten Year Incidence of Stroke in African Americans by Age and Sex: Cardiovascular Health Study

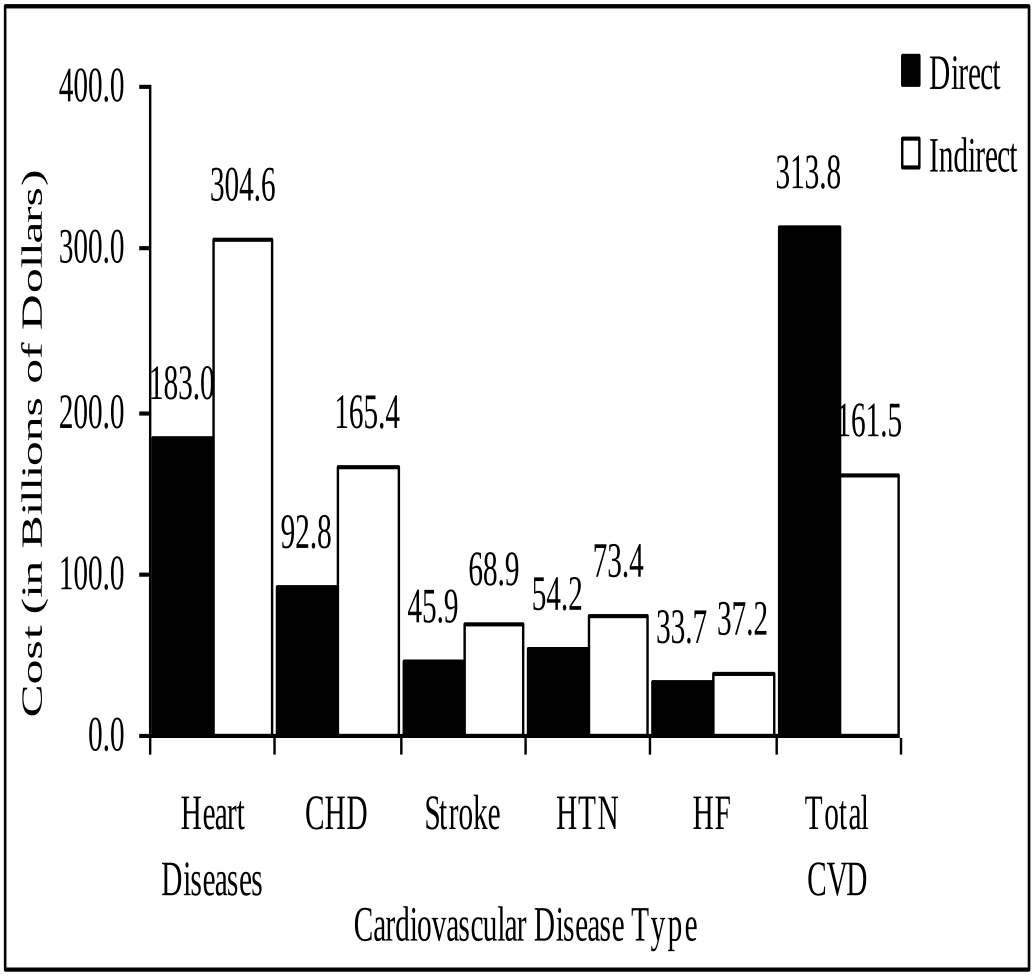

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Figure 1.13 Estimated Cost of Cardiovascular Diseases and Stroke

2.0 ASSOCIATION BETWEEN SIX MINUTE WALK DISTANCE AND ALL-CAUSE MORTALITY, CORONARY HEART DISEASE-SPECIFIC MORTALITY, AND INCIDENT CORONARY HEART DISEASE

Manuscript in preparation

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2.1 ABSTRACT

Introduction: Exercise fitness assessed by treadmill exercise testing is an independent predictor of morbidity and mortality in middle-age and older adults. However, little has been reported on the utility of submaximal walking testing, such as the six-minute walk test (6 MWT), in predicting outcomes among older adults. ***Objective:*** To determine whether the 6 MWT distance is an independent predictor of all-cause mortality, coronary heart disease(CHD)-specific mortality, and incident CHD in a large cohort of community-dwelling older adults. ***Methods:*** We conducted a time-to-event analysis of the 4,708 Cardiovascular Health Study (CHS) participants, a well-characterized cohort of older adults from 4 U.S. communities. The 6 MWT was conducted during clinic visit from June 1996 to May 1997, and completed by 2,116 participants. Additionally, 163 partially completed, and 1,052 did not attempt the 6 MWT test, while 1,377 did not have an in-person annual study exam. Events were determined after a mean follow-up time of 7.3 years. ***Results:*** The mean age at the time of the 6 MWT was 77.4 years; and the mean 6MWT distance was 343.5 meters. During follow-up, there were 793 all-cause deaths, and 187 CHD-specific deaths among participants with a 6 MWT. Among the 1,822 without prevalent CHD at the time of 6 MWT, 347 incident CHD events occurred. Event rates (per 1000 person-years) were 47.6 for all-cause mortality, 11.2 for CHD-specific mortality, and 27.6 for incident CHD. In age- and sex-adjusted models, participants in the lowest 6 MWT distance quintile (<279 meters) were at increased risk of all-cause mortality (adjusted Hazard Ratio (HR), 3.0; 95% Confidence Interval (CI), 2.4-3.8), CHD-specific mortality (adjusted HR, 2.4; 95% CI, 1.5-3.8) and incident CHD (adjusted HR, 1.6; 95% CI, 1.2-2.3). In a fully adjusted

model, participants with a 6MWT performance in the lowest two distance quintiles remained at a greater risk of all-cause mortality (6 MWT 279-333 meters: adjusted HR 1.6; 95% CI, 1.2-2.2; 6 MWT <279 meters: adjusted HR 1.9; 95% CI, 1.4-2.5). The inverse relationship between 6 MWT performance and all-cause mortality remained in analyses stratified by age, sex, and race. The increased risk of CHD-specific mortality and incident CHD observed in the lowest 6 MWT distance quintile (<279 meters) was attenuated, by 65.5% and 71%, respectively, after adjustment for confounders (CHD-specific mortality adjusted HR, 1.4 (95% CI, 0.8-2.4); incident CHD adjusted HR, 1.2 (95% CI, 0.8-1.8). ***Conclusion:*** The 6 MWT was an independent predictor of all-cause mortality in community-dwelling older adults.

2.2 INTRODUCTION

Physical fitness, as measured by exercise duration or oxygen uptake, has been shown to predict cardiovascular events and all-cause mortality in middle-aged and older adults populations[1-7]. Treadmill-based and walk-based testing represent alternate methods for the assessment of functional exercise capacity[8]. While the treadmill exercise test has been the most commonly applied method for the assessment of exercise capacity, older adults encounter greater limitations in their ability to complete a treadmill based exercise test[9]. Moreover, the submaximal performance during a walking test in older adults may be a better reflection of daily activities and a more practical method of assessment than treadmill-based protocols[10-12]. While performance on walking test such as the 6-Minute Walk test (6 MWT) has been shown to be of prognostic significance in various disease-specific patient populations, there is limited information on the prognostic value of the 6 MWT in community-dwelling older adults.

The 6 MWT is a simple, safe, and easily administered test which has been studied in various disease specific populations, such as those with pulmonary disease, heart failure, pacemakers, peripheral arterial disease, and organ transplant candidates[13-20]. In older adult populations the 6 MWT is a reliable and valid measure of functional capacity[21]. We investigated the prognostic value of the 6 MWT performance in community-dwelling older adults. More specifically, we aimed to determine whether the performance distance in a 6 MWT would be predictive of all-cause mortality, coronary heart disease-specific mortality, and incident coronary heart disease.

2.3 METHODS

2.3.1 Population

The CHS is an observational study with the primary goal of determining the risk factors for and consequences of cardiovascular disease in older adults. The design and methods of the CHS have been previously described elsewhere[22, 23]. Briefly, 5,888 community-dwelling older adults were recruited for CHS, including 5,201 participants recruited in 1989-1990 and an additional 687 minority predominant participants were recruited between 1992-1993. Recruitment was from a random sample of the Health Care Finance Administration Medicare eligibility lists in four communities: Forsyth County, North Carolina; Sacramento County, California; Washington County, Maryland; and Pittsburgh(Allegheny County), Pennsylvania. Annual clinic visits and semi-annual telephone and clinic contacts included standardized assessments of participant health history and behaviors, cardiovascular risk factors, measures of subclinical cardiovascular disease, cognitive and physical function. The 6 MWT was conducted during the CHS in-person examination performed between June 1996 and May 1997. The 6 MWT exclusion criteria included the presence of pre-test electrocardiogram (ECG) abnormalities, use of ambulatory aids, presence of aortic stenosis, heart rate less than 50 beats per minute or greater than 110 beats per minute, systolic blood pressure greater than 200 mm Hg or diastolic blood pressure greater than 110 mm Hg, or a myocardial infarction, angioplasty, coronary artery bypass surgery, new chest pain, dyspnea, fainting, a resting oxygen saturation less than 90%, or at the discretion of the technician. Of the 4,708 participants who remained enrolled in CHS between June 1996 and May 1997, 1,377 had a phone or proxy interview and did not have an in-person study visit. Of the 3,331 with an in-person study visit, there were 2116 participants who completed, 163 partially completed, and 1052 were either excluded due to the above listed exclusion criteria (n=764), or did not attempt the 6 MWT by either refusing testing (n=39), stating physically inability (n=34), lacking sufficient time (n=2), at technician discretion (n=28), or providing other reasons (n=30), while the remaining did not participate in the 6 MWT for unknown reason (n=155).

2.3.2 Six Minute Walk Test

The 6 MWT was conducted according to a standard protocol similar to the American Thoracic Society guidelines[24]. Briefly, in a 100 foot section of an internal hallway with distance marked every five feet by colored tape along the baseboard, participants were instructed to "walk at their own pace" up and down the hallway while attempting to cover as much ground as possible. This was the only difference between the CHS protocol for the 6 MWT and the American Thoracic Society guidelines where 6 MWT participants are encouraged to "cover as much distance as possible in 6 minutes". Technicians encouraged the participants with the standardized statements, such as "you are doing well" or "keep up the good work," but were asked not to use other phrases. Participants were allowed to stop and rest during the test, but were instructed to resume walking as soon as they could. If a participant stopped and refused to continue the test before the six minutes had elapsed, the distance walked was recorded and the walk was coded as a partial test. The technician used a mechanical lap counter to count the number of laps completed, and an electronic timer with a buzzer that sounded the completion of the 6 minutes. While oxygen saturation and pulse rate were recorded prior to the exercise, the technicians did not walk with participants and did not record the pulse oximetry readings during the walk.

2.3.3 Potential Confounders

CHS exams were extensive and included risk factors and potential confounding or mediating variables of age, sex, race, cigarette smoking status (current vs. former or never), education level (less than high school vs. more than high school), history of treated hypertension or diabetes, weight (kilograms), height (meters), waist circumference (cm), systolic blood pressure (mm Hg), total cholesterol (mg/dL), and fasting glucose (mg/dL)[22]. Cognitive function was assessed with the Mini-Mental Status Exam[25] and depressive symptoms using the Center for Epidemiological Studies Depression (CES-D) score[26]. Also assessed were limitations in the Activities of Daily Living (ADL) (any vs. no limitation), Instrumental Activities of Daily Living (IADL) (any vs. no limitation), self-reported general health status (fair or poor vs. good, very good, or excellent health). Major ECG abnormalities included ventricular conduction defects, major Q or QS abnormalities, minor Q or QS with ST-T-wave abnormalities, left ventricular hypertrophy, isolated major ST-T-wave abnormalities, atrial fibrillation, or first degree atrioventricular block were determined by a centralized ECG Reading Center according to a standard protocol[27]. The ankle arm index (AAI) was measured by trained technicians according to a standard protocol[28]. Prevalent CHD, CHF, stroke, TIA, and intermittent claudication were ascertained using methods previously described[29]. Chronic pulmonary disease was defined as a history of chronic bronchitis, emphysema, or asthma. Arthritis of the knees or hips was assessed by self-report.

2.3.4 Outcomes

The detailed methods used by the CHS for surveillance and ascertainment of mortality and cardiovascular events have been previously described[30]. Participants were contacted every 6 months in regards to interim hospitalizations and clinical visits for cardiovascular diagnoses including myocardial infarction (MI), angina, congestive heart failure (CHF), stroke, transient ischemic attack (TIA), and peripheral artery disease. An incident coronary heart disease (CHD) was defined as MI, angina, or coronary revascularization. Mortality was documented by death certificates, inpatient records, nursing home or hospice records, physician questionnaires, and autopsy reports. A CHD-specific mortality was defined to include death from CHD and sudden death. All deaths and cardiovascular events were adjudicated by a CHS committee using a standardized protocol.

2.3.5 Statistical Analysis

Analysis of variance or Kruskal Wallis test for continuous variable and Chi Squared test for categorical variables were used to test differences in participant characteristics across the 6 MWT completion status groups and 6 MWT distance quintiles, as appropriate. The 6 MWT distance was categorized into quintiles of > 411 meters, 368 to 411 meters, 333 to 368 meters, 279 to 333 meters, and to 279 meters. Crude event rates for each outcome were calculated and reported per 1000 person-years. Cox proportional hazard regression models were used to determine hazard ratios for the outcome of all-cause mortality, CHD-specific mortality, and incident CHD. Hazard ratios were estimated for the 6 MWT completion status groups and separately per quintile of 6 MWT distance with the longest 6 MWT distance quintile (> 411 meters) serving as the referent group. The hazards models were initially adjusted for age and sex, and subsequently for other confounders in fully adjusted models. In addition, separate stratified Cox proportional hazards models assessed whether the direction or magnitude of the association between 6 MWT performance and study endpoints varied by age (<80 vs. ≥ 80 years), race (white vs. non-white), sex, and self-reported general health status (fair or poor vs. good, very good, or excellent health).

Statistical analyses were conducted using STATA 11.1 (STATA Corporation, College Station, TX). All reported p values are based on a two-sided test with $P < 0.05$ considered statistically significant.

2.4 RESULTS

Participant characteristics by clinic visit and 6 MWT status revealed that those with 6 MWT attempt were younger, more often men, of white race, or of higher education level; taller in height, of lower body weight; less reported depressive symptoms; less often report inability to perform any ADLS or IADLS; higher cognitive function score; and were less likely to have prevalent health conditions or subclinical disease compared to those without a clinic visit (TABLE 2.1). The characteristics of participants with a 6 MWT attempt, either partial or complete, is shown in TABLE 2.2. While there was no significant difference in body weight across 6 MWT distance quintiles, the remaining characteristics revealed a more favorable characteristic profile among those with 6 MWT in the longer distance quintiles. Participant characteristics among those without prevalent CHD by 6 MWT completion status and distance quintiles are shown in TABLE 2.3 and TABLE 2.4, respectively. Overall, the pattern of association observed in participants without prevalent CHD was similar to that found among participants with prevalent CHD.

Among the 4,708 participants in the study cohort, there were a total of 2,286 deaths from all causes of which 556 deaths were attributed to coronary heart disease. A total of 754 incident

CHD events occurred during follow-up among the 3,441 participants free of prevalent CHD. Figures 2.1-2.6 show the Kaplan Meier survival curves for the outcomes of all-cause mortality, CHD-specific mortality, and incident CHD by clinic visit and 6 MWT status. The overall all-cause mortality rate was 74.4 per 1000 person-years and was lower among participants who either completed or partially completed the 6 MWT as compared to without a 6 MWT either with or without a clinic visit (TABLE 2.5). This difference was attenuated after adjustment for age and sex, yet remained significant with hazard ratio greater than 1.0 for participants without a 6 MWT and those without a clinic visit. After further adjustment for all potential confounders, the hazard ratio remained significant for participants without a clinic visit (HR 1.9; 95% CI:1.3-2.7) while a trend was observed for increased hazard for participants with a clinic visit but without a 6 MWT (HR 1.1; 95% CI: 1.0-1.3). The overall rate of CHD-specific mortality was 18.1 per 1000 person-years. A greater than two-fold CHD-specific mortality rate was observed in participants without a clinic visit compared to those completing a 6 MWT during their clinic visit. The hazard ratio for CHD-specific mortality for was greater than 1.0 in participants without a 6 MWT or a clinic visit after adjusting for age and sex but no longer significant in fully adjusted model (TABLE 2.5).

Incident CHD was evaluated among the 3,441 participants without prevalent CHD. A total of 754 incident CHD events were observed over the follow-up time with an overall event rate of 35.1 per 1000 person-year. Participants without a clinic visit and those with a clinic visit but without a 6 MWT had a nearly one and a half fold higher rate of incident CHD than those who had a clinic visit and either partially or fully completed the 6 MWT. While the higher risk among participants without a 6 MWT with or without a clinic visit remained significant in an age and sex adjusted model, after adjusting for all confounders the hazard ratios for incident CHD were no longer statistically significant (TABLE2.5).

Among 2,279 participants who attempted a 6 MWT (TABLE 2.6), there were 793 deaths due to all causes with the majority of the deaths 512(64.5%) due to non-cardiovascular etiology. Of the 793 deaths, 281(35.4%) were due to cardiovascular diseases with 187(66.5%) secondary to coronary heart disease. Among the participants with a 6 MWT, a distance in the two shortest distance quintiles (walk distance 279-333 meters and <279 meters) was associated with an increased hazard of all-cause mortality relative to a 6 MWT distance >411 meters. This higher risk of all-cause mortality remained in models adjusting for age and sex (walk distance 279-333 meters; crude event rate, 58.1 vs. 27.0 per 1000 person-years; adjusted HR, 2.1; 95% CI, 1.7-2.7: walk distance <279 meters; crude event rate, 80.6 vs. 27.0 per 1000 person-years; adjusted HR, 3.0; 95% CI, 2.4-3.8). In a fully adjusted model, participants with a 6MWT distance in the poorest two performance quintiles remained at higher risk of all-cause mortality (walk distance 279-333 meters; adjusted HR, 1.6; 95% CI, 1.2-2.2: walk distance <279 meters; adjusted HR, 1.9; 95% CI, 1.4-2.5). The inverse association between 6 MWT distance and all-cause mortality persisted in separate analyses when stratified by sex, race, age (65-80 vs. ≥80 years), and subclinical cardiovascular disease status (either major ECG abnormality or AAI<1.0).

In sex-stratified analysis, the multivariable adjusted hazard ratios for the association between 6 MWT performance and all-cause mortality in women were HR 2.0 (95% CI, 1.0-3.1) for 6 MWT distance 0-279 meters, HR 1.6 (95% CI, 1.0-3.0) for 279-333 meters, HR 1.1 (95% CI, 0.7-1.7) for 333-368 meters, and HR 1.1 (95% CI, 0.7-1.8) for 368-411 meters relative to 6 MWT distance >411 meters. Similarly in sex-stratified analysis, the multivariable adjusted hazard ratios for men were HR 1.8 (95% CI, 1.2-2.7) for 6 MWT distance 0-279 meters, HR 1.7

(95% CI, 1.2-2.7) for 279-333 meters, HR 1.5 (95% CI, 1.0-2.2) for 333-368 meters, and HR 1.2 (95% CI, 0.8-1.8) for 368-411 meters relative to 6 MWT distance >411 meters. In age-stratified analysis, the multivariable adjusted hazard ratios for the association between 6 MWT performance and all-cause mortality in participants aged 65-80 years were HR 1.9 (95% CI, 1.3-2.7) for 6 MWT distance 0-279 meters, HR 1.7 (95% CI, 1.2-2.4) for 279-333 meters, HR 1.1 (95% CI, 0.8-1.6) for 333-368 meters, and HR 1.1 (95% CI, 0.8-1.6) for 368-411 meters relative to 6 MWT distance >411 meters. In age-stratified analysis, the multivariable adjusted hazard ratios for participants aged ≥ 80 years were HR 2.5 (95% CI, 1.5-4.5) for 6 MWT distance 0-279 meters, HR 2.1 (95% CI, 1.2-3.7) for 279-333 meters, HR 1.8 (95% CI, 1.0-3.1) for 333-368 meters, and HR 1.3 (95% CI, 0.7-2.3) for 368-411 meters relative to 6 MWT distance >411 meters. In race-stratified analysis, the adjusted hazard ratios for all-cause mortality in non-non-white participants were HR 1.5 (95% CI, 0.5-4.3) for 6 MWT distance 0-279 meters, HR 0.9 (95% CI, 0.3-2.7) for 279-333 meters, HR 0.9 (95% CI, 0.3-3.0) for 333-368 meters, and HR 1.7 (95% CI, 0.5-5.1) for 368-411 meters relative to 6 MWT distance >411 meters. The adjusted risk for participants of white race was HR 1.9 (95% CI, 1.4-2.6) for 6 MWT distance 0-279 meters, HR 1.7 (95% CI, 1.3-2.3) for 279-333 meters, HR 1.3 (95% CI, 0.9-1.7) for 333-368 meters, and HR 1.1 (95% CI, 0.8-1.5) for 368-411 meters relative to 6 MWT distance >411 meters. Persons reporting a good or excellent general health had an adjusted HR 3.5 (95% CI, 1.4-9) for 6 MWT 0-279 meters, HR 2.3 (95% CI, 0.9-6.2) for 279-333 meters, HR 1.5 (95% CI, 0.6-4.2) for 333-368 meters, and HR 1.9 (95% CI, 0.7-5) for 368-411 meters relative to a 6 MWT > 411 meters. Those reporting poor or fair health had a HR 1.8 (95% CI, 1.3-2.5) for 6 MWT 0-279 meters, HR 1.8 (95% CI, 1.3-2.4) for 279-333 meters, HR 1.3 (95% CI, 0.9-1.8) for 333-368 meters, and HR 1.1 (95% CI, 0.8-1.5) for 368-411 meters relative to a 6 MWT distance > 411 meters.

Of 793 all-cause deaths among the 2,279 with a 6 MWT, 187(23.6%) were attributed to CHD with an overall CHD-specific death rate of 11.2 per 1,000 person-years. A 6 MWT distance in the shortest two quintiles was associated with a greater than 1.5-fold unadjusted CHD-death risk relative to 6 MWT performance >411 meters. After adjusting for age and sex, the two shortest 6 MWT quintiles remained at higher risk for CHD-specific mortality (walk distance 279-333 meters; crude event rate, 13.9 vs. 8.4 per 1000 person-years; adjusted HR, 1.8; 95% CI, 1.1-2.8: walk distance <279 meters; crude event rate, 18.2 vs. 8.4 per 1000 person-years; adjusted HR, 2.4; 95% CI, 1.5-3.8). Further adjustment for prevalent medical conditions and limitations in daily activities resulted in an attenuation of CHD-specific mortality risk observed in the 6 MWT distance 279-333 meters (adjusted HR, 1.4; 95% CI, 0.8-2.4) while there remained a higher risk of CHD-specific mortality for 6 MWT distance <279 meters (adjusted HR, 1.8; 95% CI, 1.0-3.1). In the fully adjusted model, the CHD-specific mortality risk associated with the two poorest 6 MWT distance quintiles was further attenuated (walk distance 279-333 meters; adjusted HR, 1.1; 95% CI, 0.6-2.0: walk distance <279 meters; adjusted HR, 1.4; 95% CI, 0.8-2.4).

Three hundred and forty-seven incident CHD events occurred among the 1,822 persons with a 6 MWT with an overall incident CHD rate of 27.6 per 1000 person-years. A 6 MWT distance in the poorest 6 MWT distance < 279 meters was associated with a higher risk of incident CHD (adjusted HR, 1.6; 95% CI, 1.1-2.3). In an age- and sex- adjusted model, a 6 MWT distance < 279 meters remained associated with an increased risk of incident CHD; crude event rate, 37.9 vs. 24.5 per 1000 person-years; adjusted HR, 1.6; 95% CI, 1.1-2.3). Further adjustment for anthropometric measures, including waist circumference, weight, and height, (adjusted HR, 1.4; 95% CI, 0.9-2.0) and in a fully adjusted model (adjusted HR, 1.2; 95% CI, 0.8-1.8) the risk of incident CHD associated with the shortest 6 MWT quintiles was further attenuated.

2.5 DISCUSSION

In a cohort of community-dwelling older adults, both the performance distance walked and participation in a 6 Minute Walk test were shown to be independent predictors of all-cause mortality. The 6 MWT distance was shown to have a strong graded relationship with all-cause mortality. Among participants with a 6 MWT distances between 279-333 meters and <279 meters, the relative risk of all-cause mortality was 63% and 89% greater than participants able to walk >411 meters. The 6 MWT was also associated with CHD outcomes but this association was explained by poorer participant health status. This study suggests the 6MWT is a useful measure of functional exercise capacity with prognostic significance and extends previous work in specific patient populations to community-dwelling older adults with a wide range of performance.

Performance on walk-based testing has been shown to be correlated with cardiorespiratory fitness[31]. In addition, both self-reported walking ability and performance on distance-based walk tests have been shown to be predictors of disability, cardiovascular morbidity, and all-cause mortality[32-34]. Performance on the Long Distance Corridor Walk (LDCW), a distance-based walking test, has been previously shown to be prognostic of morbidity and mortality in older adults[33]. While distance-based walking tests have the advantage of providing participants with motivation in order to maintain a faster gait speed, they are limited in their ability of capturing the performance of persons who fail to complete the full distance of the test[35,36]. In contrast, time-based walking tests, such as the 6 MWT, allow the capture of performance by all who are tested regardless of whether the participant walked for the full allotted time period. This unique advantage of time-based walking tests allows the capturing of walking distance of those with very low level of walking performance. As for the relationship between the 6 MWT and health outcomes, the inverse association has previously been demonstrated in disease-specific populations, including patients with heart failure, pulmonary disease, and end stage liver disease[37-41]. More recently a smaller study of 217 Finish women examined the relationship of 6 MWT performance and participation with all-cause mortality and found that participating in a 6 MWT to be a significant predictor of mortality[42].

Several strength and limitations of our study noteworthy. First, the performance during a 6 MWT may not reflect an individual's maximal oxygen uptake. Second, approximately one-third of the participants with a clinic visit did not perform a 6 MWT and in separate analyses we did reveal that lack of participation in the clinic visit and 6 MWT was prognostic. The strengths of our study include its large sample size, long follow-up time, standardized surveillance and ascertainment of hard outcomes, and a cohort of older adults with a wide spectrum of function and health condition.

The conventional method for the assessment of cardiorespiratory or exercise capacity is via exercise treadmill testing and our finding of an inverse relationship between all-cause mortality and functional exercise capacity is consistent with well-established literature using treadmill-based measurement of exercise capacity[2-7, 43]. Although the treadmill exercise test is considered the "gold standard", it has several limitations including requiring clinical oversight by trained personnel, has associated equipment costs, and safety concerns. Alternatively, the 6 MWT is a valid and reliable method of physical endurance assessment which can be performed by many older adults[21,44]. Our findings suggests that the 6-Minute Walk test, as a measure of physical fitness and overall health, is an independent predictor of all-cause mortality in older adults.

2.6 REFERENCES FOR CHAPTER 2

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2.7 TABLES FOR CHAPTER 2

Table 2.1 Participant characteristics by study visit and Six Minute Walk test participation status

Characteristics*	Visit Done, Completed 6MWT (n= 2116)	Visit Done, Partial Completers 6MWT (n= 163)	Visit Done, No 6MWT (n= 1052)	No Visit, No 6 MWT (n= 1377)	P Value
Age, yr	77.4±4.3	77.9±4.5	79.0±5.3	80.7±5.8	<.001
Male	853(40.3)	54(33.1)	425(40.4)	483(35.1)	.004
Non-white	305(14.4)	34(20.9)	22(21.6)	252(18.3)	<.001
Education(< high school)	472(22.3)	37(22.7)	283(26.9)	492(35.7)	<.001
Body mass index, kg/m^2	26.7±4.2	27.8±6.0	27.2±5.2	26.7±5.7	.07
Weight, kg	72.0±13.6	73.5±17.4	72.9±15.6	68.6±16.8	0.001
Height, m	1.6±0.1	1.6±0.1	1.6±0.1	1.6±0.1	<.001
SBP, mm Hg	136.0±19.4	133.9±19.4	138.6±23.1	138.9±20.5	.01
CHD	413(19.5)	44(27.0)	344(32.7)	466(33.8)	<.001
CHF	114(5.4)	10(6.1)	161(15.3)	252(18.3)	<.001
Stroke	78(3.7)	9(5.5)	115(10.9)	187(13.6)	<.001
TIA	59(2.8)	9 (5.5)	53(5.0)	88(6.4)	<.001
Claudication	47(2.2)	9(5.5)	45(4.3)	77(5.6)	<.001
Diabetes	281(13.3)	24(14.7)	177(16.8)	115(8.4)	<.001
Arthritis	576(28.5)	57(36.5)	426(42.7)	293(37.5)	<.001
Pulmonary disease	260(12.7)	31(19.6)	178(17.6)	127(15.7)	.001
Any ADL limitation	231(11.0)	17(10.6)	348(34.4)	292(42.3)	<.001
Any IADL limitation	504(23.8)	52(31.9)	534(51.5)	385(54.7)	<.001
Current Smoker	134(6.4)	19(11.9)	88(8.6)	72(9.1)	.01
Fair or Poor Health	263(12.6)	34(20.9)	303(29.3)	416(38.8)	<.001
CES-Depression	5.2±4.4	5.9±4.6	7.1±5.3	7.1±6.2	<.001
Mini-MMSE	93.2±7.5	91.4±10.4	88.2±13.5	75.1±21.8	<.001
Major ECG Abnormality	598(28.8)	60(37.5)	433(42.8)	174(54.9)	<.001
AAI (< 1.0)	303(15.0)	34(21.8)	216(22.1)	283(29.3)	<.001
Total cholesterol, mg/dL	202.4±39.1	196.3±36.0	201.7±40.5	204.5±45.4	.22
Fasting glucose, mg/dL	104.7±28.8	109.2±37.7	109.0±36.2	115.3±41.2	.001
Medication use					
Aspirin	120(5.7)	8(4.9)	77(7.4)	70(8.2)	.04
Any anti-hypertensive	1106(52.3)	98(60.1)	710(67.9)	533(62.2)	<.001
Any Lipid Lowering	254(12.0)	22(13.5)	105(10.0)	65(7.6)	.003

* Presented as mean ± SD or n(%).

Abbreviations: 6 MWT refers to 6 Minute Walk Test; yr, year; SBP, systolic blood pressure; CHD, coronary heart disease; CHF, congestive heart failure; TIA, transient ischemic attack; ADL, activities of daily living; IADL, independent activities of daily living; MMSE, Mini-Mental Status Exam; ECG, electrocardiogram; AAI, ankle arm index

Table 2.2 Characteristics by quintile (range in parentheses) of Six Minute Walk test distance(meters)

Characteristics	(>411) n= 448	(368 - 411) n= 462	(333 - 368) n= 455	(279 - 333) n= 454	(0 - 279) n= 460	P Value
Age, yr	76.2±3.3	76.8±4.0	77.3±4.2	78.1±4.4	78.8±5.0	.001
Male	243 (52.0)	199 (44.6)	175 (38.5)	153 (33.5)	137 (30.2)	<.001
Nonwhite	37 (7.9)	57 (12.8)	74 (16.3)	82 (17.9)	89 (19.6)	<.001
Education(<high school)	56(12.0)	83 (18.6)	103 (22.6)	130 (28.5)	137 (30.2)	.001
Body mass index, kg/m^2	25.8±3.4	26.4±3.8	26.7±4.0	27.3±4.6	27.6±5.4	<.001
Weight, kg,	72.2±12.7	72.1±13.4	72.1±13.2	72.1±14.0	71.8±16.2	0.70
Waist Size, cm	93.7±10.9	96.0±11.8	95.7±11.7	98.1±12.9	99.2±14.6	.001
Height, m	1.7±0.1	1.6±0.1	1.6±0.1	1.6±0.1	1.6±0.1	<.001
Systolic blood pressure	133.5±18.3	136.4±18.5	135.3±19.7	136.4±19.0	137.7±21.3	.02
CHD	88(18.8)	77(17.3)	85(18.7)	100(21.9)	107(23.6)	.11
CHF	19 (4.1)	18 (4.0)	16 (3.5)	30(6.6)	41(9.0)	.001
Stroke	8 (1.7)	13 (2.9)	12 (2.6)	23 (5.0)	31(6.8)	<.001
TIA	8(1.7)	11(2.5)	13(2.9)	13(2.8)	23(5.1)	.04
Claudication	3 (0.6)	10(2.2)	7(1.5)	10(2.2)	26(5.7)	<.001
Diabetes	40(8.6)	61(13.7)	63(13.9)	61(13.4)	80(17.6)	.002
Arthritis	99(22.4)	85(20.1)	119(27.6)	171(38.7)	159(36.6)	<.001
Pulmonary disease	55(12.2)	45(10.3)	38(8.7)	73(16.7)	80(18.2)	<.001
Any ADL limitation	22 (4.7)	37 (8.3)	47(10.4)	62 (13.8)	80(18.1)	<.001
Any IADL limitation	53 (11.4)	70(15.7)	108(23.7)	145(31.8)	180(39.7)	<.001
Current Smoking	21(4.6)	29(6.6)	33(7.3)	30(6.7)	40(9.0)	.12
Fair or Poor Health	23(4.9)	33(7.5)	61(13.5)	72(16.0)	108(24.0)	<.001
CES-Depression	4.2±3.9	4.6±4.1	5.5±4.6	5.6±4.7	6.2±4.9	<.001
Mini-MMSE	95.9±4.8	93.9±6.8	93.5±7.1	92.0±8.1	90.1±9.9	<.001
Major ECG Abnormality	114(25.0)	115(26.2)	124(28.1)	142(31.6)	163(36.4)	.001
AAI (< 1.0)	30(6.6)	46(10.8)	54(12.4)	87(20.2)	120(27.9)	<.001
Total cholesterol, mg/dL	195.7±37.8	204.3±40.3	202.2±36.9	206.1±38.1	201.5±41.0	.001
Fasting glucose, mg/dL	100.1±22.6	103.3±26.0	106.0±30.7	106.5±31.3	109.1±34.8	.001
Medication use						
Aspirin	24(5.1)	26(5.8)	25(5.5)	30(6.6)	23(5.1)	.86
Any anti-hypertensive	196(42.4)	215(48.2)	246(54.1)	246(53.8)	299(65.9)	<.001
Any Lipid Lowering	62(13.2)	51(11.4)	59(12.9)	57(12.5)	47(10.4)	.65

* Presented as mean ± SD or n(%).

Abbreviations: 6 MWT refers to 6 Minute Walk Test; yr, year; SBP, systolic blood pressure; CHD, coronary heart disease; CHF, congestive heart failure; TIA, transient ischemic attack; ADL, activities of daily living; IADL, independent activities of daily living; MMSE, Mini-Mental Status Exam; ECG, electrocardiogram; AAI, ankle arm index

Table 2.3 Participant characteristic without prevalent CHD by clinic visit and six minute walk test status

Characteristics	Visit Done, Completed 6MWT (n= 1,703)	Visit Done, Partial Completers 6MWT (n= 119)	Visit Done, No 6MWT (n= 708)	No Visit, No 6 MWT (n= 911)	P Value
Age, yr	77.3±4.3	77.6±4.5	79.0±5.2	80.4±5.9	<.001
Male gender	614(36.1)	35(29.4)	264(37.3)	278(30.5)	.01
Nonwhite	260(15.3)	25(21.0)	156(22.0)	175(19.2)	.0004
Education(<high school)	375(22.0)	24(20.2)	188(26.6)	305(33.5)	<.001
Body mass index, kg/m^2	26.7±4.2	27.7±6.1	27.5±5.5	26.4± 5.6	.03
Weight, kg	71.5±13.5	73.3±18.4	73.3±16.1	67.4±16.2	<.001
Height, m	1.6±0.1	1.6±0.1	1.6±0.1	1.6±0.1	.001
Waist size, cm	96.3±12.4	98.4±17.1	98.6±15.3	98.2±14.7	.01
SBP, mm Hg	136.4±19.5	133.8±18.6	139.2±22.1	140.1±20.7	.002
CHF	45(2.6)	1(0.8)	53(7.5)	79(8.7)	<.001
Stroke	46(2.7)	4(3.4)	61(8.6)	100(11.0)	<.001
TIA	40(2.4)	5(4.2)	30(4.2)	38(4.2)	.03
Claudication	25(1.5)	4(3.4)	16(2.3)	24(2.6)	.13
Diabetes	201(11.8)	13(10.9)	116(16.4)	63(6.9)	<.001
Arthritis	449(27.7)	41(35.7)	295(43.8)	177(34.1)	<.001
Pulmonary disease	208(12.7)	25(21.4)	114(16.6)	74(13.8)	.01
Any ADL limitation	185(11.0)	14(11.9)	232(34.2)	178(38.4)	<.001
Any IADL limitation	380(22.3)	35(29.4)	341(49.0)	245(51.9)	<.001
Current Smoking	114(6.8)	14 (12.1)	65(9.3)	55(10.3)	.01
Fair or Poor health	188(11.1)	21(17.7)	181(26.1)	235(33.2)	<.001
CES-Depression	5.0±4.4	5.8±4.7	7.0±5.3	7.1±6.1	<.001
Mini-MMSE	93.2±7.4	91.9±10.8	88.2±14.2	74.3±23.1	<.001
Major ECG Abnormality	402(24.0)	32(27.1)	239(34.7)	91(45.5)	<.001
AAI (< 1.0)	212(13.1)	22(19.1)	117(17.7)	171(26.6)	<.001
Total cholesterol, mg/dL	203.8±38.6	196.5±38.0	202.2±41.7	211.0±44.3	.03
Fasting glucose, mg/dL	103.3±27.2	105.2±34.0	109.0±37.0	110.3±33.6	.02
Medication use					
Aspirin	72(4.2)	4(3.4)	38(5.4)	36(6.2)	.18
Any anti-hypertensive	803(47.2)	60(50.4)	413(58.8)	314(54.4)	<.001
Any Lipid Lowering	146(8.6)	15(12.6)	43(6.1)	31(5.4)	.01

* Presented as mean ± SD or n(%).

Abbreviations: 6 MWT refers to 6 Minute Walk Test; yr, year; SBP, systolic blood pressure; CHD, coronary heart disease; CHF, congestive heart failure; TIA, transient ischemic attack; ADL, activities of daily living; IADL, independent activities of daily living; MMSE, Mini-Mental Status Exam; ECG, electrocardiogram; AAI, ankle arm index

Table 2.4 Characteristics of participants without prevalent CHD by quintile (range in parentheses) of Six Minute Walk test distance(meters)

Characteristics*	(>411) n= 379	(368 - 411) n= 369	(333 - 368) n= 370	(279 - 333) n= 357	(0 - 279) n= 347	P Value
Age, yr	76.1±3.4	76.6±3.9	77.2±4.1	78.1±4.4	78.6±5.0	<.001
Male	180 (47.9)	145 (39.5)	129 (35.3)	102 (29.0)	58 (23.9)	<.0001
Nonwhite	28 (7.5)	47 (12.8)	65 (17.8)	67 (19.0)	53 (21.8)	<.0001
Education(< high school)	43(11.4)	70 (19.1)	86 (23.6)	96 (27.2)	80 (32.9)	<.0001
Body mass index, kg/m^2	25.6±3.4	26.4±3.8	26.7±4.0	27.5 ± 4.6	27.7 ±5.4	<.001
Waist size, cm	93.4±10.9	95.9±11.9	95.3±12.0	98.5±13.2	99.3±14.9	<.001
Weight, kg	71.2±12.5	71.5±13.3	71.4±13.1	72.3±14.1	71.6±16.3	0.88
Height, m	1.7±0.1	1.6±0.1	1.6±0.1	1.6±0.1	1.6±0.1	<.001
SBP, mm Hg	133.3±18.5	136.6±18.5	135.8±19.6	137.0±18.7	138.9±21.6	.001
CHF	5(1.3)	6(1.6)	7(1.9)	9(2.5)	19(7.5)	.01
Stroke	2(0.5)	9(2.4)	7(1.9)	16(4.5)	16(4.6)	.001
TIA	8(2.1)	7(1.9)	10(2.7)	6(1.7)	9(4.0)	.31
Claudication	2(0.5)	4 (1.1)	4(1.1)	5(1.4)	14(4.0)	.01
Diabetes	25(6.6)	49(13.3)	44(11.9)	41(11.5)	55(15.9)	.002
Arthritis	74(20.6)	69(19.9)	95(27.2)	131(37.6)	121(36.2)	<.001
Pulmonary disease	60(12.9)	34(9.5)	29(8.2)	60(17.6)	63(18.7)	. <.001
Any ADL limitation	18(4.8)	30(8.1)	39(10.6)	47(13.4)	65(19.2)	<.001
Any IADL limitation	40(10.6)	52(14.1)	82(22.2)	108(30.3)	133(38.3)	<.001
Current Smoking	16(4.3)	26(7.2)	33(9.0)	25(7.2)	28(6.3)	.13
Fair or Poor health	15(4.0)	23(6.3)	49(13.3)	47(13.4)	75(21.9)	<.001
CES-Depression	4.3±4.0	4.6±4.1	5.3±4.4	5.4±4.5	6.0±4.9	<.001
Mini-MMSE	95.9±4.9	93.7±7.1	93.5±6.8	92.1±8.2	90.3±9.8	<.001
Major ECG Abnormality	81(21.5)	76(20.8)	87(24.2)	88(25.1)	102(29.7)	.05
AAI (< 1.0)	18(4.9)	29(8.2)	40(11.4)	60(18.0)	87(26.5)	<.001
Total cholesterol, mg/dL	197.5±36.4	205.1±39.6	203.6±37.1	207.1±37.4	203.7±42.0	.01
Fasting glucose, mg/dL	99.4±22.6	102.8±25.5	104.5±30.2	103.7±25.2	106.8±33.3	.02
Medication use						
Aspirin	13(3.4)	14(3.8)	15(4.1)	18(5.0)	16(4.6)	.83
Any anti-hypertensive	141(37.2)	161(43.6)	182(49.2)	169(47.3)	210(60.52)	<.001
Any Lipid Lowering	33(8.7)	28(7.6)	37(10.0)	31(8.7)	32(9.2)	.84

***** Presented as mean ± SD or n(%).

Abbreviations: 6 MWT refers to 6 Minute Walk Test; yr, year; SBP, systolic blood pressure; CHD, coronary heart disease; CHF, congestive heart failure; TIA, transient ischemic attack; ADL, activities of daily living; IADL, independent activities of daily living; MMSE, Mini-Mental Status Exam; ECG, electrocardiogram; AAI, ankle arm index

Table 2.5 Event Rates and Hazard Ratios for Total Mortality, CHD-Specific Mortality, and Incident CHD Events by Visit and 6 Minute Walk Test Status

				Hazard Ratio (95% Confidence Interval)		
Events	**No. Participants**	**No. Events**	**Events per 1000 Person-Years**	**Unadjusted Model**	**Age- and Sex-Adjusted**	**Multivariable Adjustment***
All-Cause Mortality	4,708	2,286	74.4			
No clinic visit	1,377	920	126.2	2.8 (2.6-3.1)	2.5 (2.3-2.8)	1.9 (1.3-2.7)
Visit, No 6MWT	1,052	573	84.7	1.9 (1.7-2.1)	1.6 (1.5-1.8)	1.1 (1.0-1.3)
Visit, Partial 6MWT	163	67	60.3	1.3 (1.0-1.7)	1.3 (1.0-1.6)	1.1 (0.8-1.5)
Visit, Complete 6MWT	2,116	726	46.7	1.0	1.0	1.0
CHD-Specific Mortality	4,708	556	18.1			
No clinic visit	1,377	219	30.1	2.8 (2.3-3.5)	2.5 (2.0-3.1)	1.3 (0.6-1.7)
Visit, No 6MWT	1,052	150	22.2	2.0 (1.6-2.5)	1.8 (1.4-2.2)	1.2 (0.9-1.5)
Visit, Partial 6MWT	163	14	12.6	1.1 (0.7-2.0)	1.1 (0.7-1.9)	0.8 (0.4-1.7)
Visit, Complete 6MWT	2,116	173	11.1	1.0	1.0	1.0
Incident CHD	3,441	754	35.1			
No clinic visit	911	226	48.5	1.8 (1.5-2.1)	1.6 (1.3-2.0)	1.0 (0.5-2.1)
Visit, No 6MWT	708	181	42.6	1.6 (1.3-1.9)	1.4 (1.2-1.7)	1.0 (0.8-1.3)
Visit, Partial 6MWT	119	20	25.1	0.9 (0.6-1.4)	0.9 (0.6-1.4)	0.9 (0.6-1.5)
Visit, Complete 6MWT	1,703	327	27.7	1.0	1.0	1.0

* Adjusted for age, sex, race, general health status, education level, smoking status, systolic blood pressure, total cholesterol, fasting glucose, waist circumference, height, weight, prevalent medical conditions (coronary heart disease, transient ischemic attack, stroke, congestive heart failure, intermittent claudication, pulmonary disease, diabetes mellitus, arthritis), any difficulty in Activities of Daily Living or Instrumental Activities of Daily Living, CES-Depression scale score, Modified Mini-Mental State score, major electrocardiogram abnormalities, ankle-brachial index, and medication use (aspirin, any lipid lowering, any anti-hypertensive).

Table 2.6 Event Rates and Hazard Ratios for Total Mortality, CHD-Specific Mortality, and Incident CHD by Quintile of Six Minute Walk Test Distance

				HR(95% Confidence Interval)		
Event	**No. Participants**	**No. Events**	**Events per 1000 Person-Years**	**Unadjusted Model**	**Age- and Sex-Adjusted**	**Multivariable Adjustment***
All-cause Mortality	2,279	793	47.6			
>411	448	100	27.0	1.0	1.0	1.0
368-411	462	124	36.4	1.4 (1.1-1.8)	1.4 (1.1-1.8)	0.9 (0.9-1.6)
333-368	455	146	43.2	1.6 (1.3-2.1)	1.6 (1.3-2.1)	1.0 (0.9-1.7)
279-333	454	188	58.1	2.2 (1.8-2.9)	2.1 (1.7-2.7)	1.6 (1.2-2.2)
0-279	460	235	80.6	3.2 (2.5-4.0)	3.0 (2.4-3.8)	1.9 (1.4-2.5)
CHD-specific Mortality	2,279	187	11.2			
>411	448	31	8.4	1.0	1.0	1.0
368-411	462	30	8.8	1.1 (0.6-1.8)	1.1 (0.7-1.8)	0.9 (0.5-1.7)
333-368	455	28	8.3	1.0 (0.6-1.7)	1.1 (0.6-1.8)	0.7 (0.3-1.2)
279-333	454	45	13.9	1.7 (1.1-2.7)	1.8 (1.1-2.8)	1.1 (0.6-2.0)
0-279	460	53	18.2	2.3 (1.5-3.6)	2.4 (1.5-3.8)	1.4 (0.8-2.4)
Incident CHD	1,822	347	27.6			
>411	379	69	24.5	1.0	1.0	1.0
368-411	369	50	18.5	0.8 (0.5-1.1)	0.8 (0.5-1.1)	0.8 (0.5-1.2)
333-368	370	77	30.1	1.2 (0.9-1.7)	1.3 (0.9-1.8)	1.0 (0.7-1.5)
279-333	357	70	29.4	1.2 (0.9-1.7)	1.2 (0.9-1.7)	1.1 (0.7-1.7)
0-279	347	81	37.9	1.6 (1.1-2.3)	1.6 (1.1-2.3)	1.2 (0.8-1.8)

* Adjusted for age, sex, race, general health status, education level, smoking status, systolic blood pressure, total cholesterol, fasting glucose, waist circumference, height, weight, prevalent medical conditions (coronary heart disease, transient ischemic attack, stroke, congestive heart failure, intermittent claudication, pulmonary disease, diabetes mellitus, arthritis), any difficulty in Activities of Daily Living or Instrumental Activities of Daily Living, CES-Depression scale score, Modified Mini-Mental State score, major electrocardiogram abnormalities, ankle-brachial index, and medication use (aspirin, any lipid lowering, any anti-hypertensive).

2.8 FIGURES FOR CHAPTER 2

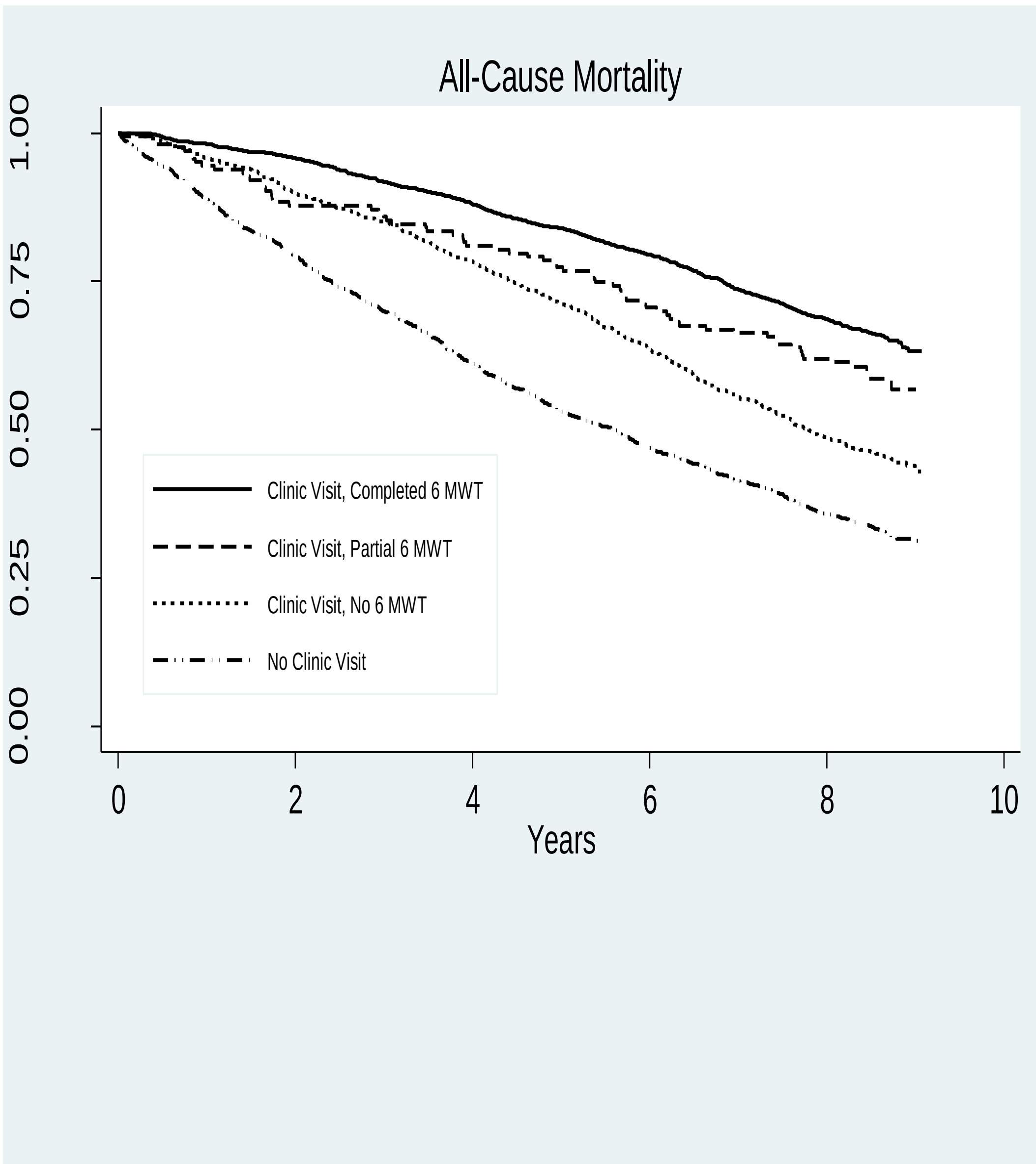

Figure 2.1 Kaplan Meier Survival Estimates of All-Cause Mortality by Clinic Visit and Six Minute Walk Test Status

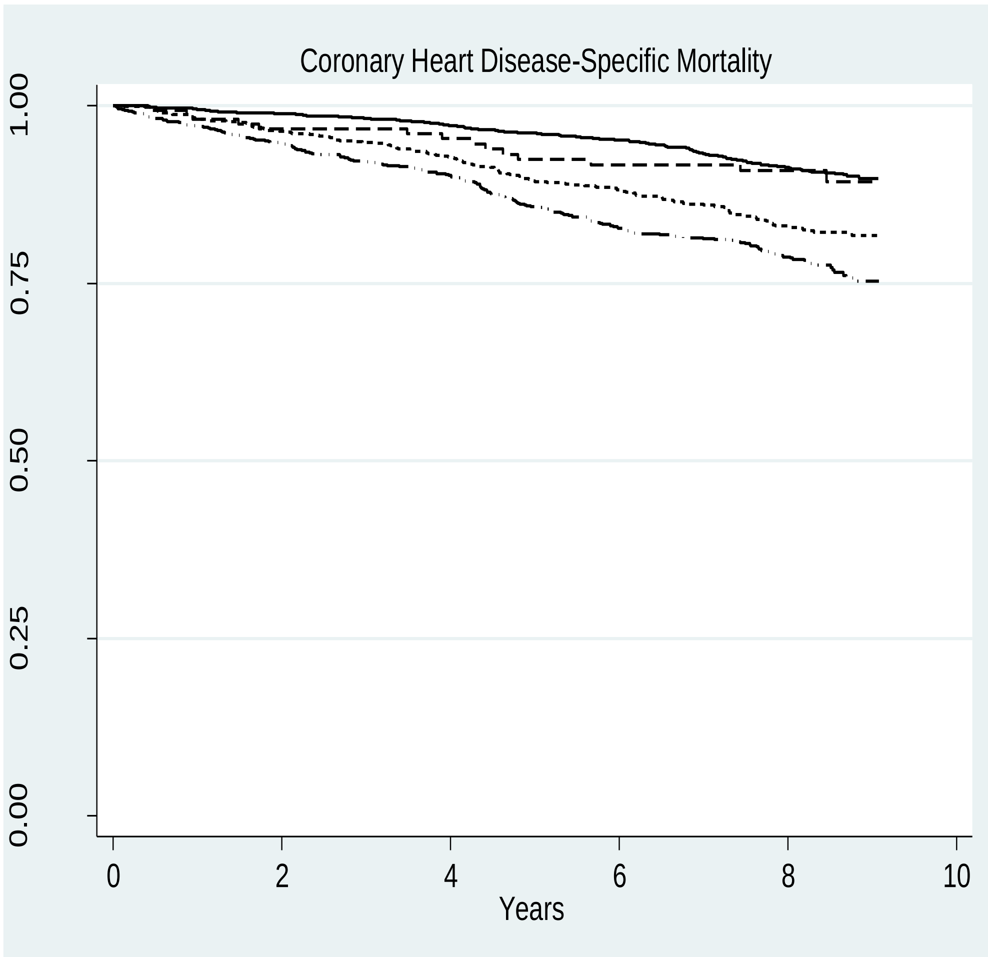

Figure 2.2 Kaplan Meier Survival Estimate of Coronary Heart Disease-Specific Mortality by Clinic Visit and Six Minute Walk Test Status

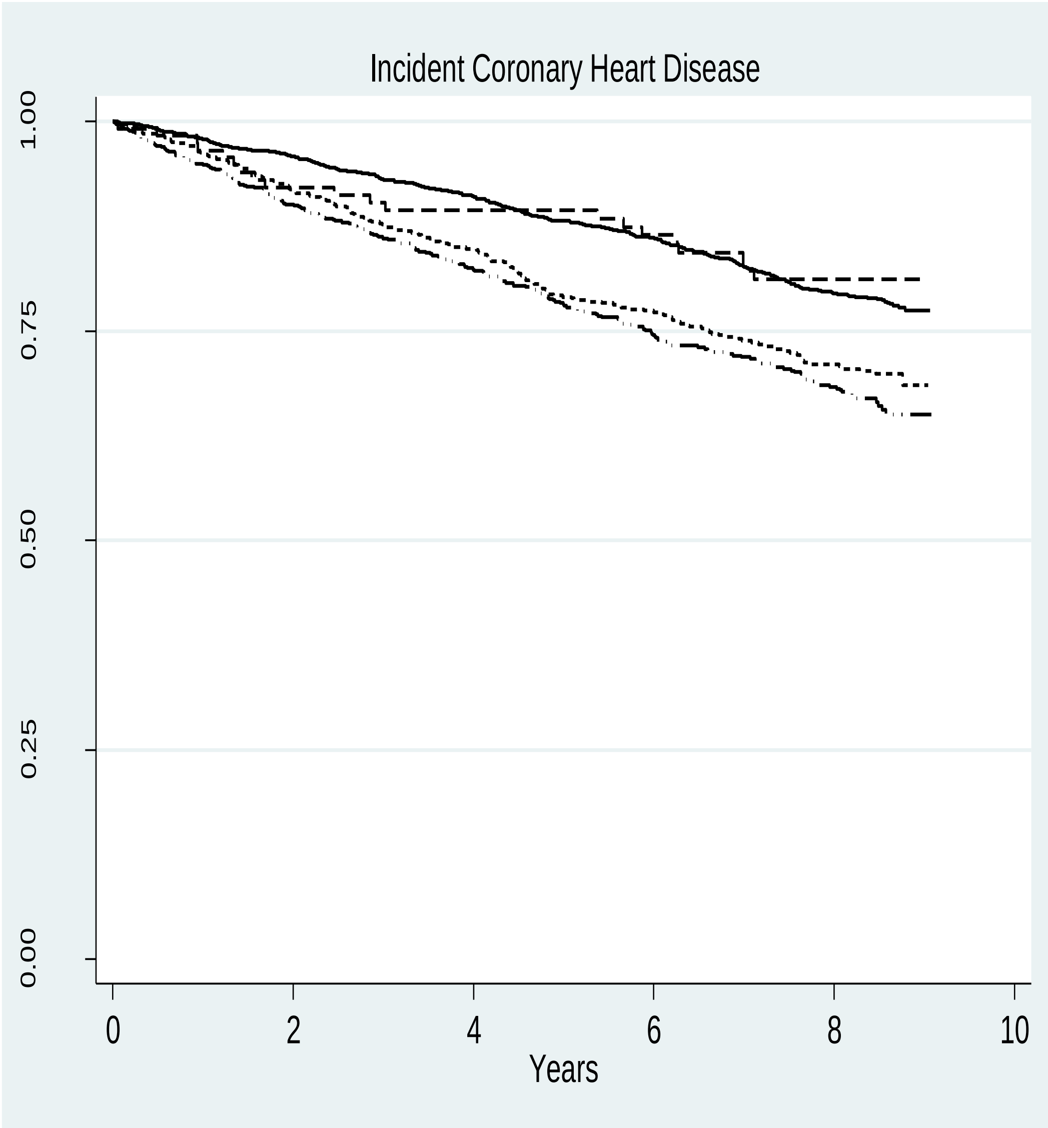

Figure 2.3 Kaplan Meier Survival Estimate of Incident Coronary Heart Disease by Clinic Visit and Six Minute Walk Test Status

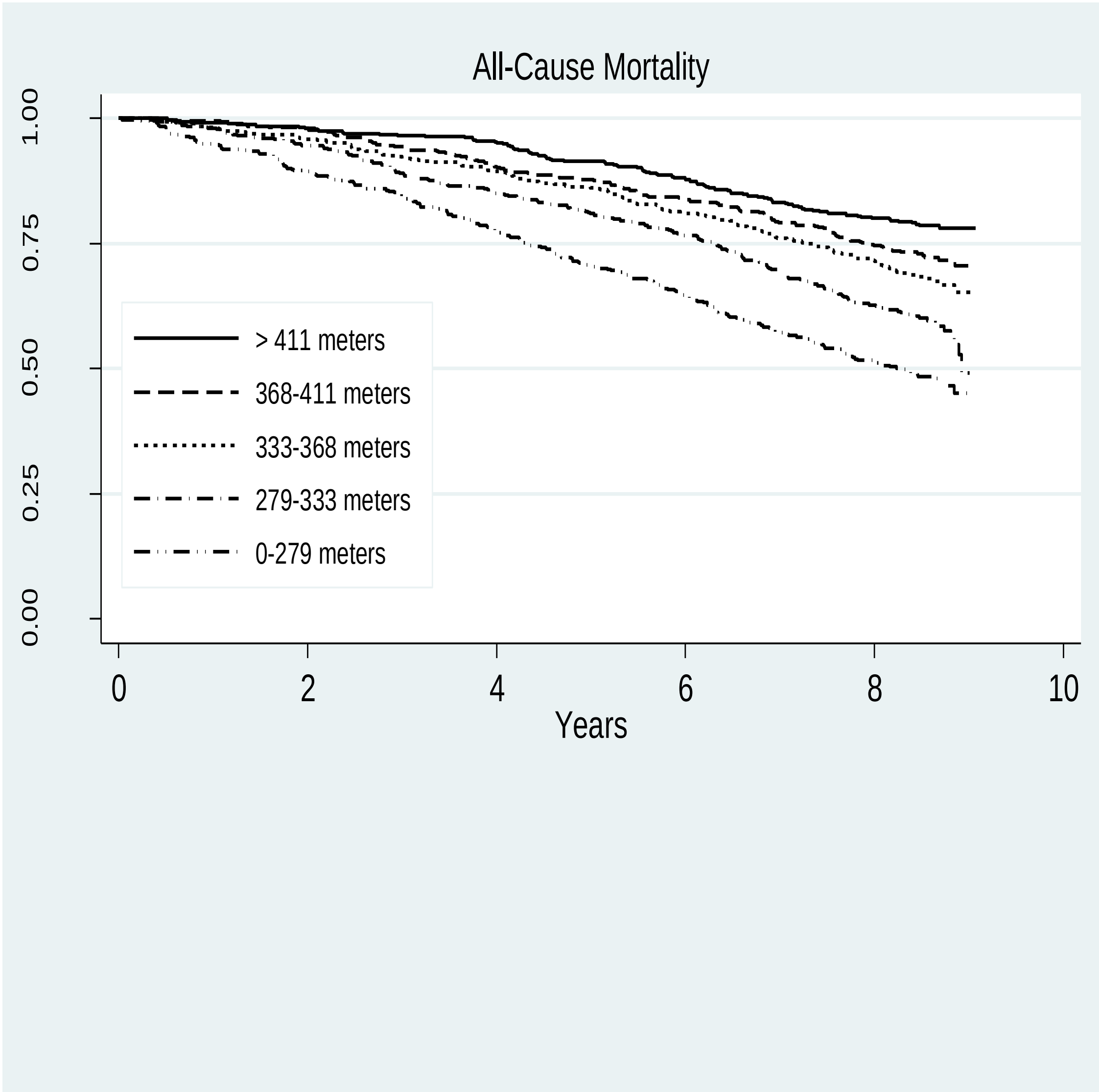

Figure 2.4 Kaplan Meier Survival Estimate of All-Cause Mortality by Quintiles of Six Minute Walk Distance

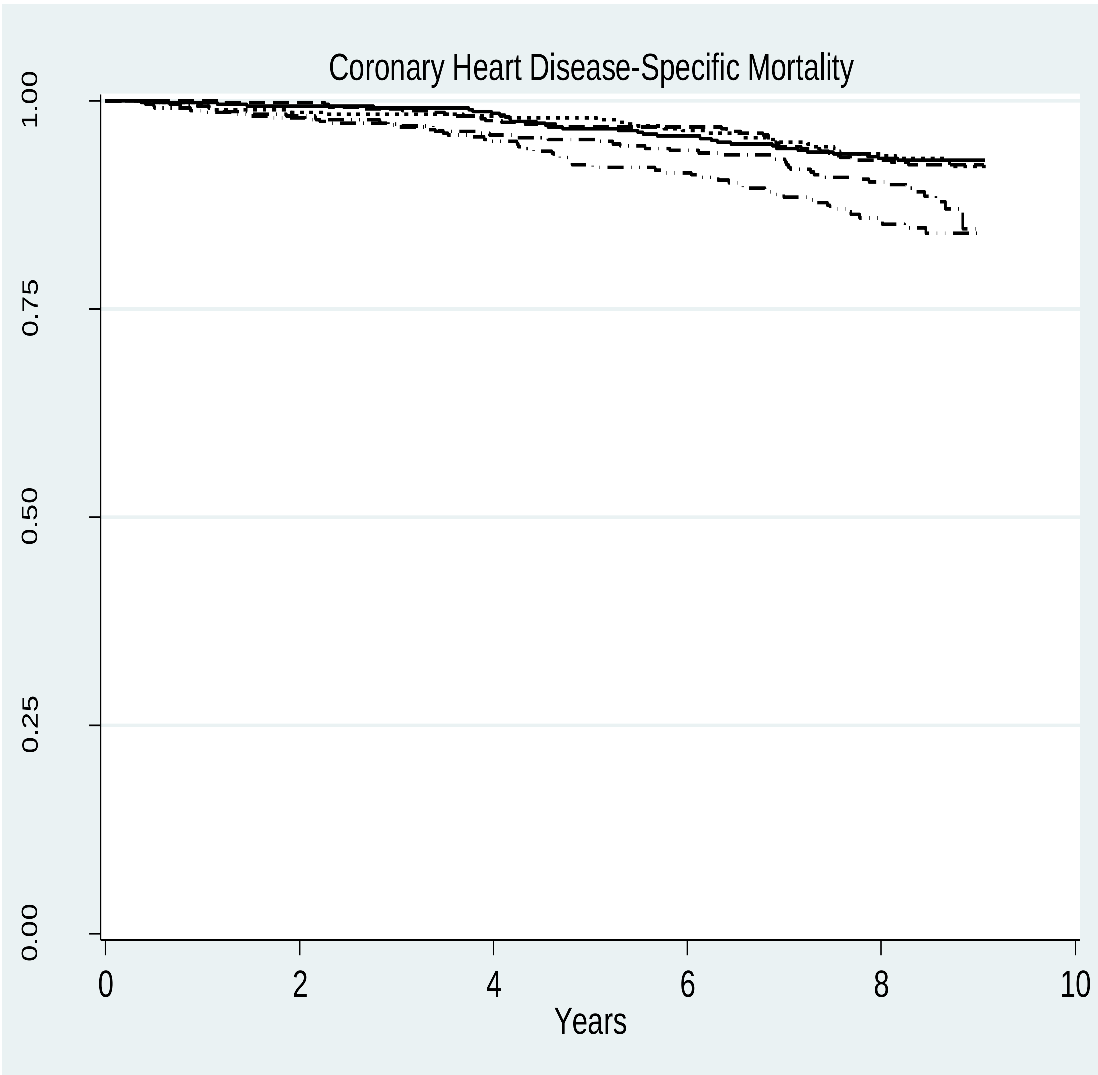

Figure 2.5 Kaplan Meier Survival Estimate of Coronary Heart Disease-Specific Mortality by Quintiles of Six Minute Walk Distance

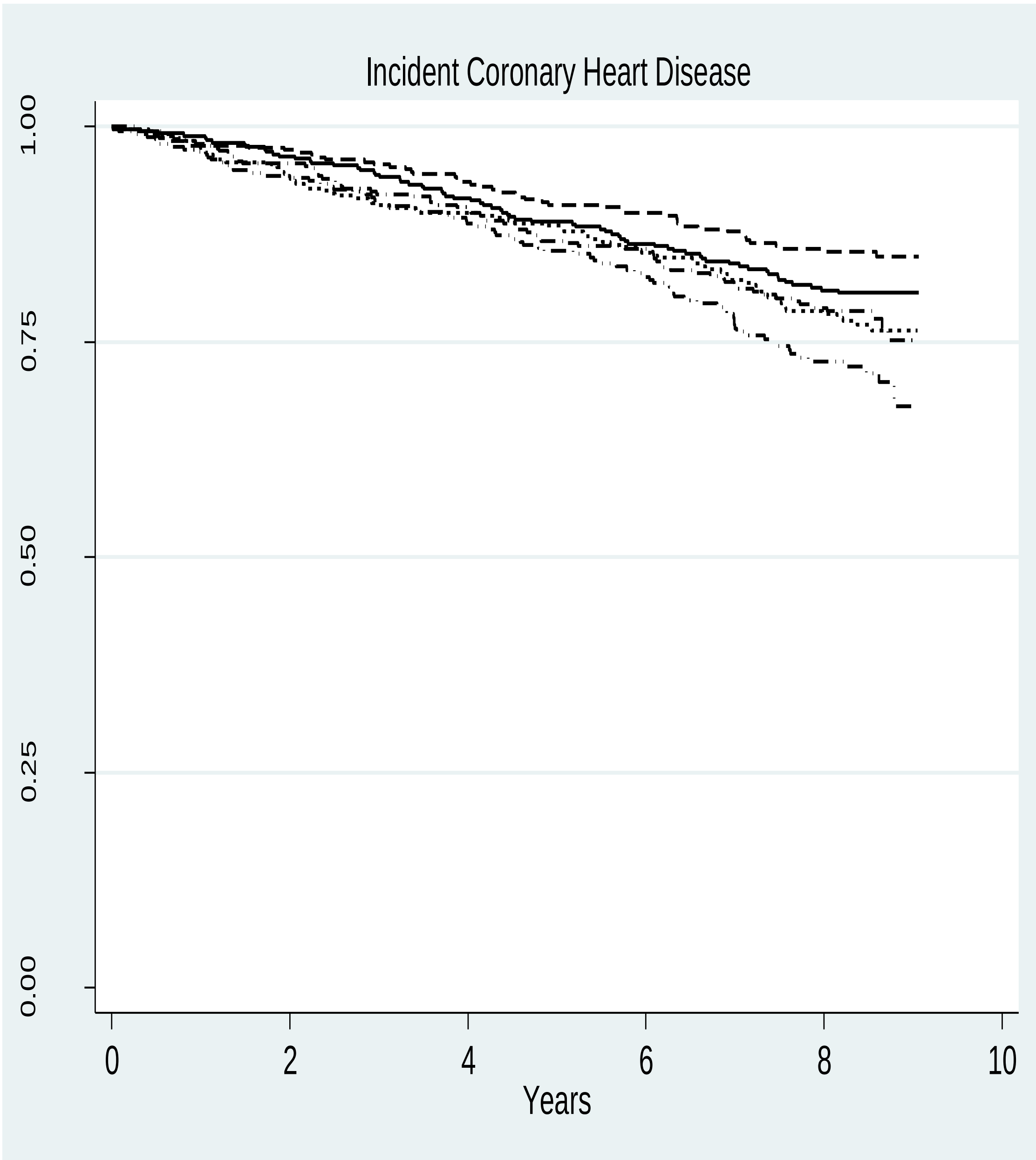

Figure 2.6 Kaplan Meier Survival Estimate of Incident Coronary Heart Disease by Quintiles of Six Minute Walk Distance

3.0 ASSOCIATION BETWEEN CORONARY ARTERY CALCFICATION AND TREADMILL EXERCISE PERFORMANCE IN COMMUNITY-DWELLING OLDER ADULTS

Manuscript in preparation

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3.1 ABSTRACT

Background: While testing for treadmill exercise capacity and coronary artery calcification(CAC) assessment are utilized in cardiovascular risk stratification, there is limited information on whether these two measures are associated in the very old as they are in the younger adults. ***Aim:*** To assess the relationship between physiologic and electrocardiographic measures based on exercise testing with CAC in a cohort of community-dwelling older adults without known clinical cardiovascular disease. Additionally, we sought to determine the characteristics of older adults associated with a more favorable performance as measured by the duration of exercise on treadmill testing. ***Methods:*** Between 2001 and 2003, 131 of 614 participants from the Arterial Calcification in the Elderly in Cardiovascular Health Study (ACE-CHS) without cardiovascular disease underwent both an Electron Beam Computed Tomography (EBT) scan and an treadmill exercise test according to a modified Balke protocol. Non-participants had prevalent cardiovascular disease(n=289), did not meet additional eligibility criteria(n=92), had interim medical illness(n=1), incomplete data(n=1), died(n=6), or refused participation(n=92). The CAC was measured with EBT scanning and the physiologic and electrocardiographic parameters during treadmill testing. Participant characteristics were compared by tertiles of treadmill exercise time. The association between physiologic and electrocardiographic findings during exercise testing across CAC score tertiles were investigated. Logistic regression determined factors associated with the outcomes of interest, including an exercise-induced ischemia as detected by an electrocardiogram and also a longer time on treadmill exercise testing. ***Results:*** The mean age of participants was 82.15±3.19 years. The mean treadmill exercise time was 4.55±2.71 minutes; the mean CAC score was 498±760 (range: 0-4210). Overall, 10 (7.73%) participants had a ischemia by electrocardiogram during exercise treadmill testing. Relative to participants with CAC<400, those with a CAC ≥400 had a greater odds of ischemia as detected by an electrocardiogram after adjusting for potential confounders (Odds Ratio [OR] 8.86;95% Confidence Interval[CI]: 1.68-46.70). While the treadmill exercise duration did not differ significantly across CAC tertiles, the presence of hypertension (OR 0.42;95% CI:0.19-0.92) and distance walked in six minutes (240 - 336 meters(m): OR 1.00 (referent); 337- 389 m: OR 3.09 (95%CI:1.07-8.83); 390 -561 m: OR 4.47 (95% CI: 1.54-12.96)) were independently associated with treadmill exercise time. ***Conclusion:*** In a cohort of community-dwelling older adults free of prevalent cardiovascular disease, there was an independent association between CAC and electrocardiogram diagnosed ischemia as induced by exercise treadmill testing but not with the duration of exercise on treadmill testing.

3.2 INTRODUCTION

Electron Beam computed tomography (EBT) is a noninvasive technique for the detection and quantification of coronary artery calcification (CAC), a reflection of the total atherosclerotic burden. While in younger aged adults there have been studies reporting on the association between CAC and various measures of its physiologic significance, including exercise testing[1, 2] and the stress single photon emission computed tomography (SPECT)[3-7], there is limited data on the physiologic significance of CAC as measured by treadmill exercise testing in community-dwelling elderly without prevalent cardiovascular disease.

Conventional classification system recognizes CAC scores of 100-399 and $\geq$ 400 as moderate and severe atherosclerosis, respectively[8]. Previous investigations of the association between CAC and stress induced myocardial ischemia utilizing perfusion imaging have suggested the presence of a CAC threshold with a greater than a two-fold increase in the frequency of stress induced ischemia when CAC $\geq$ 400 are compared to CAC of 100-399[3,4]. In older adults, a significant proportion exceed this threshold of CAC, with 59% of older men and 36% of older women having CAC $\geq$ 400[9]. While the age-related increase in the prevalence and extent of CAC has been recognized, the relationship between the extent of CAC and stress testing physiologic and ischemic parameters in community-dwelling older adults is unknown.

Given the additional utility of the exercise treadmill testing in providing valuable insight regarding functional capacity beyond electrocardiographic ischemic changes[10,11], we investigated the relationship of CAC, as measured by EBT scan, with exercise duration on treadmill testing and also with exercise-induced ischemia, as detected by an electrocardiogram, in a cohort of community-dwelling older adults without prevalent cardiovascular disease.

3.3 METHODS

3.3.1 Population

The Cardiovascular Health Study (CHS) and Arterial Calcification in the Elderly in Cardiovascular Health Study (ACE-CHS) design and methods have been previously described elsewhere[9,12,13]. Between 2001 and 2003, 131 participants from the CHS Pittsburgh field center who were free of clinical cardiovascular disease at time of assessment underwent both an EBT and exercise treadmill testing.

Participants from the original ACE-CHS cohort (1998-2000) without cardiovascular disease, including a myocardial infarction, angina, transient ischemic event, stroke, intermittent claudication, valve heart surgery, peripheral or cardiac revascularization, cardiac device implantation, and also participants with cognitive or physical mobility impairment were excluded. Cardiovascular events were ascertained every 6 months either by phone contact or at the clinical examination, validated by medical record review, and adjudicated by committee[14]. Of the 614 original ACE CHS participants, 289(47%) had CVD, 39(6%) had either a physical or cognitive limitation and/or no longer community-dwelling, 53(15%) were unable to walk on treadmill (8.6%), 92 refused study participation, 5(1%) died during study , 2(0.3%) had interim medical illness after start of study, and 3(0.5%) were not able to have their CVD status confirmed or had scheduling conflicts.

3.3.2 Coronary Artery Calcification

Coronary artery calcification was assessed using an Imatron C-150 EBT scanner and the Agatston scoring method[15], as previously described[9].

3.3.3 Exercise Treadmill Test

Participants performed a graded exercise test according to a modified Balke protocol in which the speed is held constant and the elevation raised in stages[16]. Briefly, the initial stage of the treadmill test began with participants walking for 2 minutes at a speed 2.0 mph and 0% grade. After this initial stage, the speed was increased to 3.0 mph at 0% grade in women, and 3.5 mph in for the men and elevation raised 3% every two minutes, until exhaustion or stop parameters are reached while maintaining the same speed. Participants unable to keep pace during *Stage 1* were excused. If the participant was able to keep pace at *Stage 1* but unable to keep pace at *Stage 2*, then the exercise testing using the Modified Balke protocol was substituted by a Modified-Modified Balke protocol.

The exercise was symptom-limited and was continued until one the following was reached:(1) the heart rate reaching the age-predicted maximum heart rate (220-age);(2) hypotensive response to exercise; (3) symptoms of moderate to severe angina; (4) volitional exhaustion; or, (5) a positive ECG concerning for exercise induced ischemia. A positive test was defined as a horizontal ST depression greater or equal to 1 mm occurring 80 milliseconds after the J-point during exercise or recovery. The exercise test was supervised and interpreted by physicians at the University of Pittsburgh Medical Center.

3.3.4 Demographics and Other Confounders

Age was assessed at time of the Electron Beam CT scan. The status of hypertension, diabetes, chronic obstructive pulmonary disease, smoking, self-reported health and arthritis were assessed at the 2001 to 2002 examination. Hypertension was defined by self-report of high blood pressure, diagnosis by a physician, or use of an antihypertensive medication. Diabetes was defined by self-report of diabetes or use of a diabetes-related medication. Chronic Pulmonary disease was defined by self-report of emphysema or asthma diagnosed by a physician. Arthritis was defined by a self-report of arthritis involving either the hips or knees. Body mass index was expressed as kilograms per meters squared (kg/m^2). Smoking status was reported as ever versus never because there were few current smokers. Gait speed was calculated from duration of time in seconds to walk a distance of 15-foot at the usual walking pace.

3.3.5 Outcomes

The outcomes of interest were both the duration of exercise on treadmill testing and also the occurrence of exercise induced-ischemia as detected by the electrocardiogram, defined as horizontal or down-sloping ST segment depression $\geq$1mm.

3.3.6 Statistical Analysis

Analysis of Variance or Kruskal Wallis test determined the association between continuous variables and tertiles of exercise duration on treadmill testing. Wilcoxon Rank Sum test or Student's t test determined the association between continuous variables and dichotomous covariates. Chi Square test was used to assess the association between categorical variables. Exercise treadmill testing ECG findings which were negative or non-diagnostic for ischemia were coded as negative ECG for ischemia whereas ECG positive for ischemia were based on definition previously described. Logistic regression determined the covariates independently associated with study endpoints. Statistical significance was defined as a two-tailed $P<0.05$. All statistical analyses were performed using STATA 11.1 (STATA Corporation, College Station, TX).

3.4 RESULTS

The duration of exercise on the treadmill and CAC was measured in 131 predominantly female (60.31%) and of white race (74.81%) community-dwelling older adults without prevalent clinical CVD. Table 3.1 displays the participant characteristics by gender. Participant mean age was 82.2 years and did not significantly different between men and women. The men were taller, heavier in weight, and had a significantly better physical performance as assessed by the 6 MWT distance and gait speed. The differences in CAC ((median, 48.9; IQR, 248.4,854.0) vs. (median,19.9; IQR, 125.0,536.0), p=0.19) did not reach statistical significance. Similarly, the proportion of participants with diabetes, hypertension, chronic pulmonary disease, arthritis, and a fair or poor general health status did not differ significantly between men and women.

The distribution of CAC in the study participants is shown in FIGURE 3.1. The median CAC score was 166.5(Inter-quartile range, 34.0,659.8) with a wide range from 0 to 4,209.97. Majority of the participants 122 (93.1%) had at least some quantity of CAC (CAC>0). Table 3.2 displays the characteristics of participants by tertile of CAC score. Participants with the higher

CAC score were significantly older and more likely to be of white race. The participant characteristics, including lifestyle, anthropometric variables, chronic health conditions, and physical performance measures did not differ significantly across tertile of CAC.

The median(Inter-quartile range) duration of exercise on the treadmill was 4.0(2.3,6.4) and did not differ significantly between men and women(P=0.64). While the resting heart rate was higher in women than men (73.38±10.67 vs. 69.15±12.63, p= 0.03), differences between the other resting and peak exercise measures, including the resting systolic blood pressure (134.71±19.17 vs. 137.35±21.35, p=0.52), resting diastolic blood pressure(74.54±9.49 vs. 76.5±9.31, p= 0.22), peak systolic blood pressure (161.44±22.48 vs. 164.29±27.32, p=0.67), peak diastolic blood pressure(82.77±13.42 vs. 83.19±12.02, p= 0.97), and the peak heart rate(126.0±15.50 vs. 125.67±14.97, p= 0.77) did not differ significantly. Overall, there were 10(7.73%) participants with exercise-induced ischemia with a non-significant difference between women and men(5(6.33%) vs. 5(9.62%), p=0.52).

Table 3.3 displays the characteristics of the participant characteristics by tertile of treadmill exercise time. After adjusting for age and sex, the factors independently associated with a treadmill performance in the highest tertile of treadmill exercise time (>5 minutes) included a longer distance walked during 6 minutes and the absence of hypertension (TABLE 3.4).

Table 3.5 displays the relationship between coronary artery calcification and treadmill exercise test physiologic and electrocardiogram measures. While the association between resting and peak exercise parameters were non-significant, there was a trend towards a higher proportion of positive exercise-induced ECG ischemic with a higher coronary artery calcification (P=0.06). Coronary artery calcification (CAC>0) was present in all (100%) participants with a exercise induced ischemia as detected by an electrocardiogram. The proportion of exercise electrocardiogram positive for ischemia by coronary artery calcification score according to a conventional categorization of no atherosclerosis (CAC=0), minimal atherosclerosis(CAC,1-10), mild atherosclerosis(CAC,11-100), moderate atherosclerosis(CAC,101-400), and extensive atherosclerosis(>400) was 0%, 7.7%, 3.3%, 2.9%,15.6%, respectively. In a multiple logistic model adjusting for the traditional risk factors, a coronary calcification score of ≥ 400 remained independently associated with a 8.86 (1.68-46.70) greater odds of an ischemic electrocardiogram response compared to a coronary artery calcification score <400 with exercise testing (TABLE 3.6).

3.5 DISCUSSION

Our study describes the relationship between the extent of coronary artery calcification as detected by EBT and both the exercise duration and exercise-induced ischemia by electrocardiogram detection during treadmill testing in community-dwelling older adults without prevalent cardiovascular disease. In agreement with prior studies of the relationship between coronary artery calcification and myocardial ischemia detected by either exercise testing[1,18] or myocardial perfusion scanning[3-5] in younger adults, our findings revealed an association between coronary artery calcification and an ischemic electrocardiogram stress testing response in a cohort of older adults without prevalent cardiovascular disease. Similarly, our findings of a lack of significant relationship between exercise duration and the presence of coronary artery calcification is also consistent with previous reports[19]. To the best of our knowledge, our study is the first to explore these relationships between the two noninvasive measures of coronary artery disease in a cohort of community-dwelling older adults without prevalent cardiovascular disease.

The assessment of coronary artery calcification as a measure of the anatomic atherosclerotic disease and the exercise treadmill testing in the evaluation for the physiological significance of atherosclerotic disease serve as noninvasive measures for individuals at risk for coronary artery disease. Previous studies investigating the relationship between exercise testing induced ischemia detected by an electrocardiogram and the presence of coronary artery calcification using fluoroscopic techniques have reported a higher proportion of positive exercise induced ST segment depression in persons with fluoroscopically detected coronary artery calcification. In a study by Langou et al, the prevalence of positive exercise ST depression in asymptomatic middle-aged men with fluoroscopically detected coronary artery calcification was reported to be 35% compared to 4% in those without coronary artery calcification[18]. In study by Alexopoulos et al, an ECG-positive for ischemia induced by an exercise test was detected in 29% of those with versus 8% of participants without flouroscopically detect coronary artery calcification[1]. In contrast to these two reports, an investigation of the relationship between EBT detected coronary artery calcification and ischemia detected by an electrocardiogram during stress testing did not reveal a significant difference in abnormal electrocardiograms across increasing coronary artery calcification scores[3]. However, in addition to the use of EBT to detect coronary artery calcification, the participants in this study were younger (mean age, 53 years), predominantly male (69%), and underwent stress testing by several different methods (Bruce protocol treadmill (86%), adenosine (11%), dobutamine (3%)). More recently, investigators have examined the relationship between the extent of coronary artery calcification as measured by EBT or multi-detector spiral computed tomography (MDCT) and the myocardial perfusion by single photon emission computed tomography(SPECT) have revealed a clear increase in the frequency of abnormal myocardial perfusion with increasing extent of coronary artery calcification.[3-5,7]. He et al reported the rate of ischemia by myocardial perfusion imaging to increase from 0% in those with coronary artery calcification score of 0, 2.6% with CAC scores 11 to 100, 11.3% with CAC scores from 101 to 399, and 46% in those with CAC scores ≥ 400[3]. Similarly, in a study by Moser et al the rate of ischemia by myocardial perfusion imaging to increase from 5% in those with coronary artery calcification score < 100, 24% with scores from 101 to 400, and 53% in those with scores > 400[4].

The exercise treadmill stress test is less sensitive than a myocardial perfusion modality in detection of the physiological significance of the extent of coronary artery calcification. Despite this limitation, our findings revealed a similar relationship between the frequency of an exercise-induced ischemia and a coronary calcification score >400. Moreover, we found that a coronary artery calcification score >400 was associated with a greater than 8-fold increase in the odds of an exercise-induced ischemia as detected by an electrocardiogram relative to coronary artery calcification score <400.

In our assessment of the relationship between the extent of coronary artery calcification and exercise duration on the treadmill, we had hypothesized that an increased burden of coronary artery calcification would lead to exercise-induced ischemia which would subsequently result in ventricular dysfunction which is associated with reduced exercise tolerance. This hypothesis was supported by literature revealing an association between subclinical cardiovascular disease and reduced left ventricular function and impaired physical function[20-24]. However, we did not find a significant relationship between coronary artery calcification and duration of exercise on the treadmill. Our results are consistent with previously published studies in both the young adult[23] and older aged adult populations.[19] In a study of 3,163 participants (mean age, 59±8 years) of the Heinz Nixdorf Recall study, who were free of established coronary artery disease, the inverse associated observed in unadjusted analyses between EBT-detected coronary artery calcification score and the mean treadmill duration was no longer significant after adjusting for age and gender[23]. Similarly, in a study of 38 asymptomatic men (mean±SD age, 59±8 years) enrolled in the South Bay Heart Watch Program who were without prior history of angina or myocardial infarction the presence of coronary artery calcification as detected by digital subtraction cardiac fluoroscopy was not associated with exercise tolerance[19]. Several factors may account for the reduced exercise capacity in the elderly, including reductions in both skeletal muscle mass, capillarization, and mitochondrial enzyme activity[25]. Diastolic dysfunction has also been shown to be inversely associated with reduced exercise capacity[26] and could potentially serve as the mechanism by which individuals with hypertension had a nearly 60% reduction in the odds of the ability to exercise a duration in the top tertile of > 5 minutes. Finally, we found the distance walked during a six minute walk to be independently associated with the odds of the ability to exercise duration in the top tertile of > 5 minutes, such that individuals who walked a distance of more than 337 meters had a more than a three-fold greater odds than those walking shorter distances. Therefore, the six minute walk distance may serve useful in the selection elderly capable of treadmill testing as a trend for a longer distance walk was observed in treadmill capable older adults in our study cohort. This observed relationship between the six minute walk distance and exercise treadmill duration in older adults highlights the need for further investigation.

Several limitations have to be acknowledged. First, it has been previously recognized that treadmill testing in elderly does not replicate real life situations[27] which may have resulted in early termination of treadmill testing prior to achieving a peak exercise capacity. Accordingly, we selected to utilize a modified Balke treadmill protocol which is most-suited for elderly individuals with a wide range of exercise capacities and has been used in other epidemiologic cohorts including the Baltimore Longitudinal Study on Aging[10]. Second, the cross-sectional design limits speculations regarding cause-effect relationship. Third, possible selection bias due to differences between participants with and without an EBT scan and/or a clinic visit for physical function assessment. Finally, more than one-half of study participants treadmill test were terminated due to lower extremity symptoms, such as fatigue, pain, or cramps, which may indicate non-cardiopulmonary may have been a limiting factor to reaching a sufficient exertion threshold to detect ischemia on the electrocardiogram.

In this study of community-dwelling older adults free of clinical cardiovascular disease at the time of EBT and treadmill testing, we demonstrated that subclinical coronary artery disease as measured by coronary artery calcification was associated with physiologically significant ischemia but not exercise duration with treadmill testing. The presence of hypertension was also inversely associated with reduced exercise capacity. These findings highlight the potential for cardiovascular risk factor modification in maintaining functional capacity which likely not only reflects physical fitness but overall the overall health status. Preventative therapies targeting cardiovascular risk factors, including lipids and blood pressure, may have a significant beneficial role extending into the oldest ages in maintaining health and thereby functional capacity.

3.6 REFERENCES FOR CHAPTER 3

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3.7 TABLES FOR CHAPTER 3

Table 3.1 Characteristics of participants overall and by gender

Characteristic*	Overall (n=131)	Men (n=52)	Women (n=79)	P Value
CAC score	166.5(34.0,659.8)	48.9(248.4,854.0)	19.9(125.0,536.0)	0.19
Age, y	82.2±3.2	82.2±3.2	82.2±3.2	0.97
Non-white Race	33(25.2)	13(25.0)	20(25.3)	0.97
BMI, kg/m^2	26.2(3.9)	25.61(3.7)	26.62(4.0)	0.15
Height, m	1.6±0.10	1.7±0.1	1.6±0.1	<0.01
Weight, kg	71.0±12.9	77.4±12.9	66.7±11.0	<0.01
Smoking	69(53.1)	30(57.7)	39(50.0)	0.39
Fair or Poor Health	37(28.2)	13(25.0)	24(30.4)	0.50
6 MWT distance, m	366.2±63.2	389.8±64.4	350.6±57.7	<0.01
Gait Speed, m/sec	0.80±0.18	0.86±0.18	0.76±0.16	<0.01
Hypertension	67(51.2)	25(48.1)	42(53.2)	0.57
Diabetes Mellitus	19(14.5)	10(19.2)	9(11.4)	0.21
Pulmonary Disease	11(8.4)	2(3.9)	9(11.4)	0.20
Arthritis	32(24.4)	12(23.1)	20(25.3)	0.77

Abbreviations: CAC refers to coronary artery calcification Agatston score; IQR, interquartile range; y, years; SD, standard deviation; n, number, %, percent; BMI, body mass index; kg, kilogram; Smoking, current or former smoker; m, meters.
*Characteristic presented as n(%), mean±sd, or median(IQR).

Table 3.2 Participants characteristics by tertile (range in parentheses) of coronary artery calcification

Characteristic*	Overall	T1 (0-80)	T 2 (81.4-407.1)	T3 (418.0-4210.0)	P Value
Age, y	82.2±3.2	81.2±3.3	82.2±3.2	83.0±2.9	0.03
White Race	98(74.8)	22(50.0)	36(81.8)	40(93.0)	<0.01
Male	52(39.7)	14(31.8)	18(40.9)	20(46.5)	0.37
BMI, kg/m^2	26.5±3.8	27.5±4.1	25.9±3.7	26.0±3.4	0.08
Height, m	1.6±0.1	1.6±0.1	1.7±0.1	1.7±0.1	0.50
Weight, kg	71.0±12.9	71.9±12.6	70.9±12.2	70.1±14.1	0.81
Smoking	69(53.1)	20(45.5)	28(65.1)	21(48.8)	0.15
6 MWT distance, m	366.2±63.2	368.2±61.6	359.3±71.9	371.1±55.9	0.66
Gait Speed, m/s	0.8±0.2	0.8±0.1	0.8±0.2	0.8±0.2	0.71
Hypertension	67(51.2)	24(54.6)	22(50.0)	21(48.8)	0.85
Diabetes Mellitus	19(14.5)	6(13.6)	7(15.9)	6(13.9)	0.95
Pulmonary Disease	11(8.4)	4(8.9)	2(4.7)	5(11.6)	0.54
Arthritis	32(24.4)	9(20.5)	13(29.6)	10(23.3)	0.60
Fair or Poor Health	37(28.2)	14(31.1)	10(23.3)	13(30.2)	0.67

Abbreviations: Treadmill capability refers to the ability to complete both the warm up and first stages of treadmill protocol; T, tertile;6 MWT, 6 Minute Walk Test; n, number; y, year; SD, standard deviation; n, number; waist size, waist circumference; %, percent; kg, kilograms; SBP, systolic blood pressure; DBP, diastolic blood pressure; m, meters; sec, seconds; CAC score, coronary artery calcification.
*Characteristic presented as n(%), mean±sd, or median(IQR).

Table 3.3 Participant characteristics by tertile of treadmill exercise duration(min) (range in parentheses)

Characteristics*	T1 (0.35- 2.7)	T2 (2.75-5.05)	T3 (5.17- 14)	P Value
CAC score	256.4(47.0,700.6)	131.8(38.1,765.5)	254.4(14.0,613.0)	0.78
Age, y	82.7±3.6	82.0±2.6	81.8±3.3	0.34
White Race	30(66.7)	34(79.1)	34(79.1)	0.30
Female	30(66.7)	23(53.5)	26(60.5)	0.45
Height, m	1.6±0.1	1.7±0.1	1.7±0.1	0.50
Weight, kg	71.9±12.6	71.0±12.2	70.1±14.1	0.81
BMI, kg/m^2	27.6±4.1	26.2±3.8	25.7±3.3	0.05
Smoking	20(44.4)	25(58.1)	21(48.8)	0.43
Resting SBP, mm Hg	134.0±19.9	139.5±21.1	133.9±19.1	0.40
Resting DBP, mm Hg	74.5±9.6	76.3±9.7	75.2±9.1	0.74
Resting HR,beats/min	72.4±10.8	72.4±12.6	70.3±11.6	0.63
6 MWT distance, m	350.2±66.2	360.1±61.7	389.0±56.0	0.01
Gait Speed, m/s	0.7±0.2	0.8±0.2	0.9±0.2	0.01
Hypertension	28(62.2)	24(55.8)	15(34.9)	0.03
Diabetes Mellitus	8(17.8)	5(11.6)	6(14.0)	0.75
Pulmonary Disease	6(13.3)	4(9.3)	6(14.0)	0.84
Arthritis	15(33.3)	11(25.6)	6(14.0)	0.10

Abbreviations: T refers to tertile; 6 MWT, 6 Minute Walk Test; n, number; y, year; SD, standard deviation; n, number; waist size, waist circumference; %, percent; kg, kilograms; SBP, systolic blood pressure; DBP, diastolic blood pressure; m, meters; sec, seconds; CAC score, coronary artery calcification Agatston score.
*Characteristic presented as n(%), mean±sd, or median(IQR).

Table 3.4 Multiple logistic model: Characteristics association with treadmill exercise duration in the longest tertile(>5 minutes)

Characteristics	OR (95% CI)	P Value
Age, per 5 y	0.75 (0.38,1.49)	0.41
Male	0.72 (0.32,1.64)	0.43
6 MWT distance(meters)		0.02
240 - 336	1.00	
337- 389	3.09 (1.07,8.83)	
390 -561	4.47 (1.54,12.96)	
Hypertension	0.42 (0.19-0.92)	0.03

Abbreviations: OR represents odds ratio; y, year; 6 MWT, 6 minute walk test.

Table 3.5 Treadmill test parameters by tertiles (range in parentheses) of coronary artery calcification

Characteristic*	Overall	T1 (0-80)	T2 (81-407)	T3 (>423)	P Value
Treadmill Time, min	4.0(2.3,6.4)	4.1(2.3,7.3)	4.1(2.3,5.2)	3.1(2.3,5.9)	0.54
Resting SBP, mm Hg	135.8±20.0	138.4±22.0	134.4±19.2	134.4±18.9	0.57
Resting DBP, mm Hg	75.3±9.4	76.0±9.8	75.2±10.4	74.8±8.2	0.83
Resting HR, beats/min	71.7±11.6	72.5±13.4	72.4±11.6	70.1±9.5	0.55
Peak SBP, mm Hg	162.6±24.5	165.9±26.7	157.6±22.6	164.3±23.6	0.25
Peak DBP, mm Hg	82.9±12.8	83.6±17.8	82.2±9.7	83.0±9.5	0.31
Peak HR, beats/min	125.9±15.2	127.6±16.0	125.3±13.2	124.7±16.6	0.64
ECG ischemia	10(7.7)	2(4.6)	1(2.3)	7(16.3)	0.06

Abbreviations: T refers to tertile; 6 MWT, 6 Minute Walk Test; n, number; y, year; sd, standard deviation; n, number; waist size, waist circumference; %, percent; kg, kilograms; SBP, systolic blood pressure; DBP, diastolic blood pressure; m, meters; sec, seconds; CAC score, coronary artery calcification Agatston score.
* Characteristic displayed as n(%), mean±SD, or median(Inter-quartile range).

Table 3.6 Simple and Multiple logistic Models: Association of characteristics with an ischemic ECG response on treadmill exercise testing

	Unadjusted OR(95%CI)	Adjusted OR (95% CI)
CAC score		
<400	1.00	1.00
≥400	5.30(1.30-21.63)	8.86(1.68-46.70)
Age, per 5 years	0.49(0.16-1.54)	0.35(0.08-1.53)
Male gender	1.57(0.43-5.73)	1.23(0.27-5.52)
BMI		
<30	1.00	1.00
≥30	1.19(0.24-6.01)	1.67(0.26-10.67)
Smoking	1.36(0.36-5.05)	0.82(0.18-3.68)
Hypertension	0.61(0.16-2.28)	0.39(0.08-1.84)
Diabetes Mellitus	4.71(1.19-18.65)	4.80(0.90-25.47)

Abbreviations: OR represents odds ration; CAC, coronary artery calcification Agatston score; BMI, body mass index.

3.8 FIGURES FOR CHAPTER 3

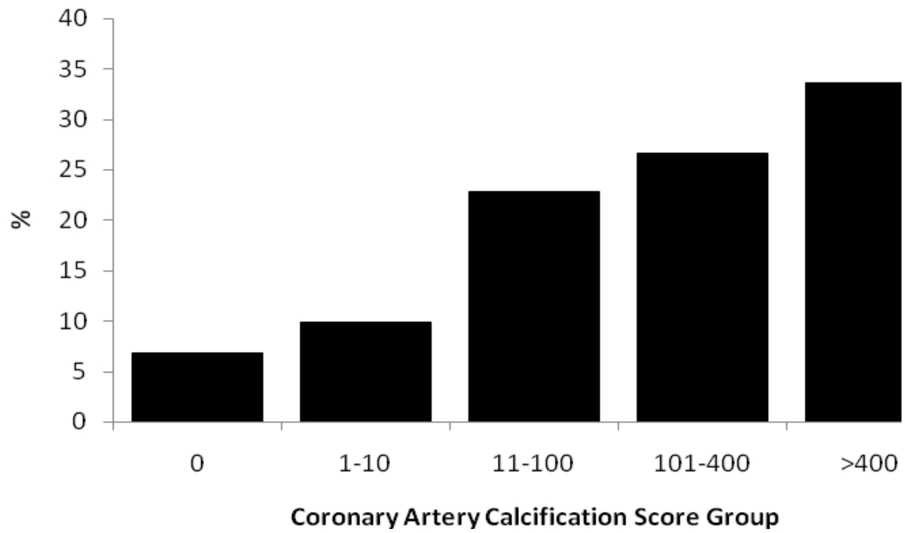

Figure 3.1 Distribution of Coronary Artery Calcification among Study Participants

4.0 ASSESSMENT OF TREADMILL EXERCISE TEST CAPABILITY AND CAPACITY USING THE SIX MINUTE WALK TEST IN COMMUNITY-DWELLING OLDER ADULTS

Manuscript in preparation

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4.1 ABSTRACT

Background: The conventional method to assess functional exercise capacity is by the treadmill exercise test yet the 6 Minute Walk test (6 MWT) has several distinct advantages especially in the community-dwelling older adult. ***Aim:*** To determine the utility of the 6 MWT in identifying community-dwelling elderly with the capability of an evaluation with treadmill testing. Additionally, we investigated the association between the 6 MWT distance and a functional capacity ≥4 Metabolic Equivalents (METs) as assessed by the treadmill exercise test. ***Methods:*** Participants of the Arterial Calcification in the Elderly (ACE) in Cardiovascular Health Study (CHS) without cardiovascular disease were evaluated for participation in a physical function and exercise testing follow-up study. A total of 205 participants had a clinic visit including a functional exercise capacity assessment with the 6 MWT and an exercise treadmill test according to a modified Balke protocol. Among the 205 participants with a clinic based assessment, 183 completed, 6 partially completed, and 16 did not have a 6 MWT. Of the 189 participants with a 6 MWT, there were 142 who were able, 35 unable, and 12 refusing the treadmill exercise test. ***Results:*** The mean age of the participants with treadmill testing was 80.8 years (female, 58%). The mean 6 MWT distance was 366.62±61.94 in tested, 351.08±76.41 refused, and 262.55±90.02 in participants who refused the treadmill exercise test(p=0.0001). In a fully adjusted model there was a nearly 3-fold increase in the odds of a participant being treadmill test capable per 100 meter increase in the 6 MWT distance (OR, 3.84 [95% CI, 1.95 to 7.60]). Of the 142 participants with a treadmill test, a total of 62 (44%) had a treadmill functional performance with an estimated MET ≥ 4. The mean 6 MWT distance was significantly greater in participants with MET≥ 4 as compared to those with MET <4 (383.82±53.58 vs. 353.30±64.96, p=0.003). After adjusting for demographics, lifestyle, and health conditions there was a nearly 2-fold increase in the odds of achieving an estimated MET ≥ 4 per 100 meter increase in 6 MWT distance (OR, 2.03 [95% CI, 1.02 to 4.03]). Walk distance of ≥ 407 meters in 6 minutes was 90.2% specific for treadmill testing capability and a 6 MWT distance ≥416 meters was 83.8% specificity for having a functional capacity of ≥ 4 MET. ***Conclusion:*** The 6 MWT is a quick and simple test useful in the selection of community-dwelling older adults capable of a conventional treadmill exercise test in addition to providing an estimate of functional exercise capacity.

4.2 INTRODUCTION

Exercise capacity is an independent predictor of all-cause and cardiovascular disease related mortality in both middle-aged and older adults[1-9]. In addition, a higher level of functional capacity has been shown to be associated with reduced healthcare costs[10]. Moreover, fitness is essential for the ability to perform daily activities with a low functional capacity serving as a predictor of disability and making independent community dwelling difficult[11-13]. Therefore, the significance of assessing functional capacity rests on its predictive ability in determining the onset of disability, health resource utilization, and adverse health outcomes.

The assessment of functional capacity in the elderly is challenging since older aged adults frequently encounter difficulties in performing a treadmill-based fitness assessment[14]. While the exercise treadmill test serves as the conventional method and gold standard for the assessment of functional capacity, the 6 Minute Walk test (6 MWT) represents an alternative that has been utilized in diverse disease-specific populations. The 6 MWT, a correlate of cardiorespiratory fitness, can be safely performed by most community-dwelling older adults[15]. The 6 MWT has several advantages over the conventional exercise treadmill test, including safety and lower cost. We aimed to determine the utility of the 6 MWT in the identification of treadmill test capable older adults. Additionally, we assessed the association between 6 MWT distance and functional exercise capacity on treadmill testing. More specifically, we investigated the association between the distance walked in 6 minutes and having a functional capacity ≥4 Metabolic Equivalents (METs) on a treadmill-based testing in a cohort of community-dwelling older adults without cardiovascular disease.

4.3 METHODS

4.3.1 Population

The Cardiovascular Health Study (CHS) and the Arterial Calcification in the Elderly in Cardiovascular Health Study (ACE-CHS) study design and methods have been previously described elsewhere[16-18]. Participants from the ACE-CHS study free of prevalent cardiovascular disease were evaluated for their eligibility to participate in a clinic based physical function and exercise testing follow-up study.

A total of 289 participants from the original ACE-CHS cohort (n=614) had interim cardiovascular disease during annual and semi-annual surveillance. A cardiovascular disease event was defined as an incident myocardial infarction, angina, transient ischemic event or stroke, intermittent claudication, and any cardiovascular-related procedures, including coronary artery bypass graft, valve heart surgery, cardiac catheterization, implanted pacemaker or defibrillator, carotid endarterectomy, and peripheral vascular angioplasty or other vascular lower-extremity surgery. Among those remaining who were excluded from study participation, there 39 persons who did not participate due to nursing home residence, presence of cognitive impairment, or a self-report of inability to walk. Lastly, two participants were excluded due to reasons related to geographic relocation and unknown CVD status.

Based on the exclusion process 284 remained eligible for the study, however, 205 had a clinic-based study visit. The remaining 79 participants were either agreeable only to a telephone interview (n=60), refused both a clinic visit and a telephone interview (n=18), or had a scheduling conflict preventing a clinic visit(n=1). There were 16 individuals excluded from the six minute walk test (6 MWT) due to use of an ambulatory aid (wheelchair, crutches, walker or cane), heart rate (HR) abnormalities (HR<50 or HR>110), severe aortic stenosis, elevated blood pressure (systolic blood pressure>200 or diastolic blood pressure>110), and/or new or worsening symptoms of chest pain, shortness of breath or fainting during the previous 2 months. Among the 205 participants with a clinic visit, 189 individuals remained eligible for a 6 MWT.

4.3.2 Six Minute Walk Test

The 6 MWT was conducted according to a standard protocol similar to the American Thoracic Society guidelines[19]. Briefly, in a 100 foot section of an internal hallway with distance marked every five feet by colored tape along the baseboard, participants were instructed to "walk at their own pace" up and down the hallway while attempting to cover as much ground as possible. This was the only difference between the CHS protocol for the 6 MWT and the American Thoracic Society guidelines where 6 MWT participants are encouraged to "cover as much distance as possible in 6 minutes". Technicians encouraged the participants with the standardized statements "You are doing well" or "keep up the good work," but were asked not to use other phrases. Participants were allowed to stop and rest during the test, but were instructed to resume walking as soon as they could. If a participant stopped and refused to continue the test before the six minutes were up, the distance was recorded and the walk coded as a partial test. The technician used a mechanical lap counter to count the number of laps completed, and an electronic timer with a buzzer that sounded the completion of the 6 minutes. While oxygen saturation and pulse rate were recorded prior to the exercise, the technicians did not walk with participants and did not observe the pulse oximetry readings during the exercise.

4.3.3 Exercise Treadmill Test

Participants performed a graded exercise test according to a modified Balke protocol in which the speed is held constant and the elevation raised in stages[20]. Briefly, the initial stage of the treadmill test began with participants walking for 2 minutes at 2.0 mph and 0% grade. After this initial stage, the speed was increased to 3.0 mph at 0% grade in women, and 3.5 mph in for the men and elevation raised 3% every two minutes, until exhaustion or stop parameters are reached, maintaining the same speed. Participants unable to keep pace during *Stage 1* were excused. If the participant was able to keep pace at *Stage 1*, but unable to keep pace at *Stage 2*, the exercise testing using the Modified Balke protocol was substituted by a Modified-Modified Balke protocol where the grade remained constant. The estimated of exercise intensity was measured in metabolic equivalents (METs) and was calculated using the American College of Sports Medicine(ACSM) walking equation[21]. The ACSM's walking equation defines METs as the rate of oxygen consumption(VO2) divided by 3.5. (VO2 was equivalent to 0.1*Speed(meter minute $^{-1}$) +1.8*Speed(meter minute^{-1})*Grade(%)+3.5).

The exercise were symptom-limited and were continued until one the following was reached:(1) the heart rate reaching the age-predicted maximum heart rate (220-age);(2) hypotensive response to exercise; (3) symptoms of moderate to severe angina; (4) volitional exhaustion; or, (5) a positive ECG concerning for exercise induced ischemia. A positive test was defined as a horizontal ST depression greater or equal to 1 mm occurring 80 milliseconds after the J-point during exercise or recovery. The exercise test was supervised and interpreted by physicians at the University of Pittsburgh Medical Center.

4.3.4 Other Covariates

Participant age was assessed at time of the clinic visit for the 6 MWT. The presence of hypertension, diabetes, chronic pulmonary disease, arthritis were assessed at the time of the most recent CHS annual examination. Hypertension was defined by self-report of high blood pressure as diagnosed by a physician or use of an antihypertensive medication. Diabetes was defined by self-report of diabetes or use of a diabetes-related medication. Chronic Pulmonary disease was define by self-report of emphysema, chronic bronchitis, or asthma as diagnosed by a physician. Arthritis was defined by a self-report of arthritis involving the hips or knees. Anthropometric measures included weight (kilograms), height (meters), and waist circumference (centimeters). Gait speed (meters per second) was calculated from the number of seconds to walk 15-feet at usual pace. The primary endpoint for the treadmill exercise test was the estimated Metabolic Equivalents (METs).

4.3.5 Statistical Analysis

Categorical and continuous variables were analyzed using Chi Squared test and t test or Wilcoxon Rank Sum test, respectively. Analysis of Variance or the Kruskal Wallis test assessed for the significance of difference in continuous variables across 6 MWT status and treadmill test capability categories. Simple and multivariable logistic regression provided an estimate of association between 6 MWT distance and a dichotomized outcome based on the participant capability of perform a treadmill exercise test (capable=1/not capable=0). Similarly, logistic regression provided an estimate of the association between 6 MWT distance and a dichotomized outcome based on exercise treadmill-based functional capacity where a good functional capacity was defined as an estimated MET $\geq$ 4. All statistical analyses were performed using STATA 11.1 (STATA Corporation, College Station, TX).

4.4 RESULTS

Participant characteristics by whether they completed, partially completed, or did not have a 6 Minute Walk Test is shown in Table 4.1. Among the 205 participants with a clinic based assessment, 183 did complete and six persons partially completed a 6 MWT. Participants who completed the 6 MWT were younger and with a faster gait speed. The characteristics of participants with a 6 MWT by whether or not they were capable of an exercise treadmill test is displayed in Table 4.2. Of the 189 with a 6 MWT, there were 142 participants who were also capable of performing the exercise treadmill test, while the others were either unable(n=35) or refused(n=12) the treadmill test. Compared with participants unable or refusing the testing, treadmill test capable participants were younger, and taller in height. The treadmill test capable had a longer 6 MWT distance and a faster gait speed compared to those unable to do a 6 MWT.

The association between the participants treadmill exercise testing capability and the 6 MWT distance based on logistic regression modeling are displayed in Table 4.3. In an unadjusted logistic model, a 100 meters increase in the 6 MWT distance was associated with an approximately 4-fold increase in the odds of a participant being treadmill test capable (OR, 4.18 [95% CI, 2.34 , 7.47]). The independent association between the 6 MWT distance and treadmill exercise testing capability remained statistically significant in an age- and sex-adjusted model with a 3-fold increased odds per 100 meter increase in 6 MWT distance (OR, 3.80 [95%

CI, 2.07 , 7.00]). After further adjusting for lifestyle and clinical factors there remained a greater than 3-fold increase in the odds of a participant being able to be treadmill tested per 100 meter increase in 6 MWT distance (OR, 3.84 [95% CI, 1.95 , 7.60]). The changes in the sensitivity, specificity, and likelihood ratio associated with several cut-offs in 6 MWT distance in the association with treadmill testing capability is displayed in TABLE 4.4. As illustrated in Table 4.4, the sensitivity of the 6 MWT decreases with longer distances walked ranging from 100% for 152.4 to 287.4 meters to 0% for 6 MWT distances greater than 560.2 meters. A distance of 407.8 to 560 meters in 6 minutes was low in sensitivity (31%), but walking this distance increased the likelihood of being capable of treadmill testing (positive LR, 2.31).

Table 4.5 displays the characteristics of the 142 participants who underwent an exercise treadmill test by functional exercise capacity. The mean age of the participants with treadmill testing was 80.8 years (female, 58%). Of the 142 participants, a total of 62 (44%) had a treadmill functional performance with an estimated MET ≥ 4. In comparison with those with poor functional performance (MET <4), individuals with a good treadmill performance (MET ≥ 4) did not differ significantly with respect to age, gender, and measures of height and waist circumference. The mean diastolic blood pressure was significantly lower in participants with estimated MET ≥ 4 (69.95 ± 8.98 vs. 74.00 ± 9.71, $p=0.01$) who were also less likely to carry a diagnosis of hypertension.

Among participants with treadmill-based estimated MET ≥ 4, the mean distance walked on the 6 MWT was significantly greater as compared to individuals with MET <4 (383.82 ± 53.58 vs. 353.30 ± 64.96, $p=0.003$). Table 4.6 displays the results of the simple and multiple logistic regression models assessing the association between the 6 MWT distance and an estimated MET ≥ 4 treadmill exercise capacity. An increase of 100 meters in the 6 MWT distance was associated with an approximately 2-fold increase in the odds of a participant having a functional capacity equivalent to an estimated MET ≥ 4 (OR, 2.32 [95% CI, 1.30 , 4.16]). The independent association between the 6 MWT distance and treadmill exercise-based functional capacity equivalent to an estimated MET ≥ 4 remained statistically significant in an age- and sex-adjusted model with a 2-fold increased odds per 100 meter increase in 6 MWT distance (OR, 2.24 [95% CI, 1.22 , 4.11]). After further adjusting for lifestyle and clinical factors there remained a greater than 2-fold increase in the odds of a participant achieving an estimated MET ≥ 4 per 100 meter increase in 6 MWT distance (OR, 2.03 [95% CI, 1.02 , 4.03]). The changes in the sensitivity, specificity, and likelihood ratio associated with several cut-offs in 6 MWT distance in the association with a participant achieving an estimated MET ≥ 4 on treadmill testing is displayed in TABLE 4.7. The specificity of the 6 MWT increased with 6 MWT distance, ranging from 0% for 240.8 to 314.6 meters to 100% for 6 MWT distances greater than 560.2 meters. For example, among the 142 participants who had a treadmill exercise test and also completed a 6 MWT, those having walked at least 416 meters during six minutes had 83.8% specificity for having a functional capacity of ≥ 4 MET.

4.5 DISCUSSION

In a cohort of community-dwelling older adults free of cardiovascular disease, the distance walked during a 6 minute was shown to be an independent predictor of treadmill exercise test capability. Additionally, the 6 MWT distance was a useful indicator of whether an older adult would have a good functional capacity as determined by a conventional treadmill based assessment. Based on our results, a distance ≥ 407 meters walked during 6 minutes has 90%

specificity in identifying whether a community-dwelling older adult would be capable of treadmill-based testing. Additionally, using a definition of good functional capacity as ≥ 4 MET, we found that a distance ≥ 416.7 meters walked during the 6 MWT was moderately specific (83.4%) for a good functional capacity. To the best of our knowledge, the application of 6 MWT distance as a tool to identify treadmill test capability and functional performance status of community-dwelling older adults without cardiovascular disease had not previously been reported.

In contrast to walking test, many elderly either do not meet eligibility criteria or are unwilling to participate in treadmill exercise testing[14]. Previous study of treadmill testing in the elderly found an age-related decline in the ability to complete a treadmill test such that by age 85 or older fewer than 10% were able to successfully complete the test[22]. Therefore, walk-based tests can serve as an alternative or as the initial test to determine whether an older aged adult may be capable of performing a treadmill based assessment.

We found the 6 MWT distance independently associated with treadmill test capability. For example, an individual able to walk at least 407.8 meters in 6 minutes would be very likely to be treadmill test capable (specificity, 90.2%). In contrast, an individual unable to walk at least 289.6 meters would be unlikely to be capable of undergoing a treadmill exercise testing.

The 6 MWT distance can also serve as a simple tool in the identification of community-dwelling older adults with a good functional capacity (MET≥4). In this aim, we provided the diagnostic characteristics of the 6 MWT distance over a range of thresholds for the determination of treadmill testing treadmill testing performance ≥4 MET. This relationship can serve an important role in the appropriate context in clinical care of the older adult. For instance, an individual's functional capacity plays a role in pre-operative cardiovascular risk assessment where a functional capacity < 4 METs may call a need for further cardiovascular testing. While a survey of an individual's self-reported ability to participate in various physical activities can provide an estimate of the functional capacity, a formal test can provide an objective measure. Based on our results, objective assessment can be provided by the 6 MWT such that the inability to walk at least 320 meters in 6 minutes would identify older adults unlikely to be have a functional capacity ≥4 MET.

Several limitations of our results are noteworthy. First, the possibility of verification or workup bias needs to be considered as study participants who were unable to complete the 6 MWT were not referred for treadmill based testing. Second, the estimation of VO_2 is less accurate and reproducible than direct measurement of VO_2. Given the correlation between VO_2 and walk-based testing is greatest in older adults and those less-fit, our findings in community-dwelling elderly may not be generalizable to other populations.

The traditional method for assessing functional capacity is via the exercise treadmill test. Although the treadmill exercise test is considered the "gold standard", it has several limitations, including the requirement for oversight by clinically trained personnel, equipment costs, and safety concerns. Additionally, the treadmill exercise testing has been reported to be impractical in the assessment of fitness in older adults[23]. Alternatively, the 6 MWT is a valid and reliable method of physical endurance assessment which can be performed by many older adults unable to perform a conventional treadmill exercise test[15,24]. Our findings, suggest that 6 MWT distance may serve as a useful tool in either the selection of elderly capable of the conventional treadmill exercise test and to provide an estimate of functional capacity for community-dwelling older adults.

4.6 REFERENCES FOR CHAPTER 4

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4.7 TABLES FOR CHAPTER 4

Table 4.1 Characteristics of Participants by Six Minute Walk Test Status

Characteristics*	No 6 MWT (n=16)	Partial 6 MWT (n=6)	Complete 6 MWT (n=183)	P Value
Age, y	83.5±3.5	83.0±4.5	81.2±3.4	0.02
Female	10(62.5)	5(83.3)	114(62.3)	0.01
Height, m	1.6±0.1	1.58±0.1	1.64±0.1	0.35
Waist Size ,cm	1.0±0.14	1.0±0.2	1.0±0.1	0.82
Weight, kg	70.3±13.5	69.9±18.7	71.2±13.6	0.94
SBP, mm Hg	139.2±18.3	123.3±11.1	134.1±17.6	0.17
DBP, mm Hg	72.7±11.5	72.5±9.7	72.0±9.9	0.97
Walking Performance Tests				
6 MWT, m	NA	197.77±111.6	351.2±73.6	<0.01
Gait Speed, m/sec	0.6±0.2	0.7±0.2	0.8±0.2	0.01
Prevalent Health Conditions				
Hypertension	15(51.7)	5(41.7)	65(45.8)	0.79
Diabetes Mellitus	2(6.9)	4(33.3)	20(14.1)	0.09
Pulmonary Disease	4(13.8)	3(25.0)	16(11.3)	0.32
Arthritis	11(40.7)	4(36.4)	33(23.4)	0.15

* Presented as mean ± SD or n(%).

Abbreviations: 6 MWT represents 6 Minute Walk Test; SD, standard deviation; NA, not applicable; n, number; y, year; cm, centimeters; n, number; waist size, waist circumference; %, percent; kg, kilograms; SBP, systolic blood pressure; DBP, diastolic blood pressure; m, meters; sec, seconds.

Table 4.2 Characteristics of Participants with Completed 6 MWT by Treadmill Test Capability

Characteristics*	Unable (n=35)	Refused (n=12)	Able (n=142)	P Value
Age, y	82.4±3.5	82.7±4.6	80.9±3.2	0.02
Female	30(85.7)	6(50.0)	83(58.5)	0.01
Height, m	1.6±0.1	1.6±0.1	1.7±0.1	0.05
Waist Size, m	1.0±0.16	1.0±0.1	1.0±0.1	0.60
Weight, kg	69.9±16.8	74.4±10.0	71.3±13.1	0.63
SBP, mm Hg	134.6±20.2	130.8±20.2	133.8±17.2	0.81
DBP, mm Hg	71.9±11.5	70.0±9.7	72.2±9.6	0.76
Walking Test Performance				
6 MWT, m	262.6±90.0	351.1±76.4	366.6±61.9	<0.01
Gait Speed, m/sec	0.7±0.1	0.8±0.2	0.8±0.2	<0.01
Prevalent Health Conditions				
Hypertension	19(54.3)	5(41.7)	65(45.8)	0.62
Diabetes Mellitus	4(11.4)	4(33.3)	20(14.1)	0.18
Pulmonary Disease	6(17.1)	3(25.0)	16 (11.3)	0.22
Arthritis	13(39.4)	4(36.4)	33(23.4)	0.15

* Presented as mean ± SD or n(%).
Abbreviations: 6 MWT represents 6 Minute Walk Test; n, number; y,year; SD, standard deviation; n, number; %, percent; kg, kilograms; SBP, systolic blood pressure; DBP, diastolic blood pressure; m, meters; sec, seconds.

Table 4.3 Association between Six Minute Walk Test Performance and Treadmill Test Capability

Characteristics	Logistic Models		
	Unadjusted	Age- and Sex-Adjusted	Fully Adjusted
6 MWT, per 100m	4.18 (2.34,7.47)	3.80 (2.07,7.00)	3.84 (1.95,7.60)
Age, per 1 y		0.93 (0.84,1.04)	0.96 (0.83,1.09)
Female		0.75 (0.31,1.79)	0.68 (0.20,2.38)
Height, per 1 cm			1.00 (0.94,1.07)
Waist circumference, per 1 cm			1.01 (0.97,1.05)
SBP, per 5 mm Hg			1.03 (0.88,1.20)
DBP, per 5 mm Hg			0.97 (0.74,1.26)
Hypertension			0.82 (0.33,2.05)
Diabetes Mellitus			1.03 (0.29,3.60)
Pulmonary Disease			1.00 (0.29,3.34)
Arthritis			0.67 (0.27,1.67)

Abbreviations: 6 MWT represents 6 Minute Walk test; cm, centimeter; y, year; SBP, systolic blood pressure; DBP, diastolic blood pressure; m, meters; sec, seconds.

Table 4.4 Association between 6 MWT Distance and Treadmill Test Capability

6 MWT Distance (m)	Sensitivity(%)	Specificity(%)	Correctly Classified (%)	LR +	LR -
152.40 - 287.43	100	0	77.60	1.00	
289.56 - 338.03	88.73	51.22	80.33	1.82	0.22
338.33 - 376.74	65.49	60.98	64.48	1.68	0.57
377.35 - 406.30	44.37	75.61	51.37	1.82	0.74
407.83 - 560.23	22.54	90.24	37.70	2.31	0.86
560.23	0	100	22.40		1.00

Abbreviations: 6 MWT refers to Six Minute Walk Test; m, meters; %, percent; LR +, Likelihood Ratio Positive; LR -, Likelihood Ratio Negative.

Table 4.5 Association between 6 MWT Distance and Treadmill Test Capacity

Characteristic*	Overall (n=142)	Metabolic Equivalents <4 (n=80)	Metabolic Equivalents ≥4 (n=62)	P Value
Age, yr	80.5±2.9	81.2±3.5	80.5±2.9	0.20
Female	83(58.5)	49(61.3)	34(54.8)	0.44
Height, m	1.7±0.1	1.6±0.1	1.7±0.1	0.28
Waist circumference, m	1.0±0.1	1.0±0.1	1.0±0.1	0.65
SBP, mm Hg	133.8±17.2	135.4±17.4	131.7±16.7	0.20
DBP, mm Hg	72.2±9.6	74.0±9.7	70.0±9.0	0.01
Walking Performance Tests				
6 MWT distance, m	366.6±61.9	353.3±65.0	383.8±53.6	0.003
Gait Speed, m/sec	0.8±0.2	0.8±0.2	0.9±0.2	0.0002
Prevalent Health Conditions				
Hypertension	65(45.8)	44(55.0)	21(33.9)	0.01
Diabetes Mellitus	20(14.1)	11(13.8)	9(14.5)	0.90
Arthritis	33(23.4)	21(26.3)	12(19.7)	0.36
Chronic Pulmonary Disease	16(11.3)	10(12.5)	6(9.7)	0.79
Modified Modified Balke Protocol	35(24.7)	25(31.3)	10(16.1)	0.04

* Presented as mean ± SD or n(%).
Abbreviations: 6 MWT represents 6 Minute Walk Test; n, number; y,year; SD, standard deviation; n, number; %, percent; kg, kilograms; SBP, systolic blood pressure; DBP, diastolic blood pressure; m, meters; sec, seconds.

Table 4.6 Association Between 6 MWT Distance and Functional Exercise Capacity

Characteristics	Logistic Models		
	Unadjusted	**Age and Sex Adjusted**	**Fully Adjusted**
6 MWT distance, per 100m	2.32 (1.30,4.16)	2.24 (1.22,4.11)	2.03 (1.02,4.03)
Age, per 1 year		0.94 (0.84,1.05)	0.90 (0.78,1.03)
Female		1.04 (0.51,2.16)	1.41 (0.41,4.78)
Height, per 1 cm			1.02 (0.96,1.09)
Waist circumference, per 1 cm			1.00 (0.96,1.04)
SBP, per 5 mm Hg			1.09 (0.94,1.26)
DBP, per 5 mm Hg			0.67 (0.51,0.88)
Hypertension			0.36 (0.15,0.88)
Diabetes Mellitus			1.01 (0.30,3.32)
Pulmonary Disease			0.80 (0.21,3.05)
Arthritis			0.71 (0.28,1.81)
Modified Treadmill Protocol			0.33 (0.12,0.89)

Abbreviations: 6 MWT represents 6 Minute Walk Test; cm, centimeter; y, year; SBP, systolic blood pressure; DBP, diastolic blood pressure; m, meters; sec, seconds.

Table 4.7 Association between 6 MWT Performance and Functional Exercise Capacity

6 MWT distance (m)	**Sensitivity (%)**	**Specificity (%)**	**Correctly Classified (%)**	**LR +**	**LR -**
240.79 - 314.56	100	0	43.66	1.00	
320.04 - 348.39	90.32	28.75	55.63	1.27	0.34
352.05 - 381.31	77.42	53.75	64.08	1.67	0.42
382.22 - 414.53	53.23	71.25	63.38	1.85	0.66
416.67 - 560.23	24.19	83.75	57.75	1.49	0.91
>560.23	0	100	56.34		1.00

Abbreviations: 6 MWT distance refers to Six Minute Walk Test; m, meters; %, percent; LR +, Likelihood Ratio Positive; LR -, Likelihood Ratio Negative.

5.0 DISCUSSION

5.1 SUMMARY OF FINDINGS

This dissertation evaluated the utility of cardiorespiratory fitness in community-dwelling older adults as it relates to subclinical cardiovascular disease and the prediction of health outcomes. Additionally, this dissertation evaluated the relationship between cardiorespiratory fitness as measured by a walk-based test and the conventional treadmill-based exercise test. All three studies measured cardiorespiratory fitness and were based on community-based older adult participants of the Cardiovascular Health Study. Chapter 2 measured cardiorespiratory fitness using a time-based walking test, the 6 Minute Walk Test. Chapters 3 and 4 included an assessment of cardiorespiratory fitness with the conventional treadmill-based exercise test.

As shown in Chapter 2, in this cohort of community-dwelling older adults, the performance distance on a 6 Minute Walk Test was an independent predictor of all-cause mortality. This study suggests the 6 Minute Walk Test is a useful measure of functional exercise capacity with prognostic significance which adds to the previous literature in disease-specific patient populations and extends its prognostic significance to community-dwelling older adults with a wide range of health and functional capacity.

The relationships between two noninvasive measures of coronary artery disease, the treadmill-based exercise test and coronary artery calcification, in a cohort of community-dwelling older adults without prevalent cardiovascular disease are displayed in Chapter 3. In this cohort, the duration of exercise on treadmill testing, a measure of cardiorespiratory fitness, was not significantly associated with the extent of coronary artery calcification. The results did reveal that the discriminatory ability of coronary artery calcification in the detection of flow-limiting coronary disease may persist in oldest old aged adults.

In the final chapter (Chapter 4), the 6 Minute Walk Test performance was shown to be a useful tool in the identification of treadmill test capable community-dwelling older adults without prevalent cardiovascular disease. Additionally, the 6 Minute Walk Test performance was useful in the determination of functional exercise capacity as measured by the conventional exercise treadmill test.

5.2 PUBLIC HEALTH SIGNIFICANCE

Given the age-related increase in the prevalence of cardiovascular diseases and other chronic health conditions, the aging of U.S. population calls for simple, safe, and low cost tools for screening and prevention of disease. Although the conventional method of using treadmill or cycle ergometry exercise testing can provide a precise assessment of fitness, walk-based testing, such as that with the 6 MWT, can serve as a more practical tool in older adults.

Taken together, our findings based on the CHS cohort provide support for the clinical application of the 6 MWT for screening purposes of community-dwelling older adults. First, the association of CAC and treadmill exercise induced ischemia may reflect the continued discriminatory ability of CAC in older adults. Secondly, the 6 MWT performance, as a reflection of cardiorespiratory fitness, can serve as a tool in the prediction of mortality. Since fitness is a marker of physical activity, the performance on the 6 MWT can assist practitioners in public health interventions aimed at promoting physical activity. Lastly, the 6 MWT performance in older adults can provide clinicians with a quick measure discriminating the treadmill capable individuals, potentially reducing healthcare resource utilization in terms of unsuccessful treadmill test referrals. Additionally, the 6 MWT performance can serve clinicians as a quick measure of functional capacity in older adults, which may aid clinicians in utilization of both appropriate healthcare and community-based resources.

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