Cardiorespiratory Fitness in Relation to Cognitive Function, Brain MRI Measures, and Quality of Life in Middle-Aged Population

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This dissertation is dedicated to my parents, my husband and my lovely daughter, for their unconditional love.

ABSTRACT

Cardiorespiratory fitness (CRF) is a well known important predictor of cardiovascular disease and overall mortality. CRF is of interest as a factor that could be intervened upon to promote health given it can be modified mainly through exercise. However, whether CRF is associated with cognitive function, brain magnetic resonance image (MRI) findings, and overall Health-related quality of life (HRQOL) in middle-aged adults is unknown.

The first manuscript tested the hypothesis that greater CRF was associated with better cognitive function 25 years later using data from the community-based Coronary Artery Risk Development in Young Adults (CARDIA) study of black and white men and women aged 18-30 at recruitment in 1985-86 (year 0). Per minute of maximal treadmill duration (Max_{dur}) of a symptom-limited treadmill test , the Rey Auditory-Verbal Learning Test (measuring verbal memory) was 0.12 words recalled higher ($P<0.0001$), the Digit Symbol Substitution Test (measuring psychomotor speed) was 0.92 digits higher ($P<0.0001$), and the Stroop Test score (measuring executive function) was 0.52 lower (better performance, $P<0.0001$). So, better cognitive function at ages 43-55 years was clearly associated with better CRF 25 years earlier.

The second manuscript evaluated the hypothesis that greater CRF is associated with lower odds of having unfavorable brain MRI findings. In the CARDIA study, the odds ratio (OR) for having less whole brain volume was 0.82 per minute higher Max_{dur} ($P=0.002$) and for having low white matter integrity was 0.85 ($P=0.03$). No significant associations were observed between Max_{dur} and normal and abnormal white matter tissue

volume. Therefore, greater CRF was associated with less brain atrophy and greater white matter integrity measured 5 years later.

The third manuscript examined the hypothesis that CRF is associated with mental and physical HRQOL and individual questions contributing to the HRQOL scores. In the CARDIA study, Max_{dur} was inversely associated with low HRQOL at year 25 with the OR for having low Mental Component Summary score (<1SD below the average in the general U.S. population) of 0.88 per minute higher of Max_{dur} ($P<0.0001$) and the OR for having low Physical Component Summary score of 0.69 ($P<0.0001$). High Max_{dur} was related to each but one individual question contributing to the HRQOL.

The projects in this dissertation support the hypothesis that CRF is associated with cognitive function, brain atrophy, white matter integrity and HRQOL, which make it possible to better identify individuals at risk for these conditions at young to middle adulthood and further suggest ways to prevent deterioration of cognition, brain structure and function, and HRQOL later in life. The findings in this project contribute evidence to the impact of CRF on brain aging and overall health in middle aged adults.

Table of Contents

List of Tables

List of Figures

A. Introduction (Note: reference citations are omitted from the Introduction; they are found in subsequent sections.)

Cardiorespiratory fitness (CRF) is the ability of the body's cardiorespiratory systems to supply oxygen during sustained physical activity. CRF level is determined by both modifiable (physical activity, smoking, obesity, and health status) and non-modifiable (age, gender, and heredity) factors, with physical activity as one of the primary modifiable determinants. Regular physical activity or exercise is found to be associated with higher or improvements in CRF (Section B2.1). Directly measured maximal oxygen uptake (VO2max) is the most precise measurement available for CRF level. Maximal treadmill duration (Max_{dur}) of a symptom-limited treadmill test is widely used as a close approximation of VO_2max obtained from a maximal treadmill test to measure CRF. However, as treadmill duration is influenced by multiple aspects of both physiologic and psychologic functioning, Max_{dur} could be considered more as a measure of the treadmill performance potential of the tested human being, rather than simply the capability of the cardiorespiratory system.

Low CRF is associated with higher risk of cardiovascular diseases and its risk factors, cardiovascular death and all-cause mortality. Changes of CRF levels are associated with morbidity and mortality. Importantly, as CRF could be modified by physical exercise, CRF will play an important role in the prevention and improvement of these medical conditions. Moreover, CRF, which is measured objectively by exercise tests, would provide a precise measurement of the body fitness level and would be helpful in correctly classifying individuals' risk for future medical conditions. Therefore, CRF is an ideal

exposure variable to assess when studying risk of certain disease or health condition.

Impaired cognitive function, which lies between normal forgetfulness and dementia, is associated with stroke and limitation in daily activities in elderly. Therefore, impaired cognitive function tends to decrease HRQOL. A better understanding of factors related to preservation and impairment of cognitive function is critical to prevent stroke and dementia and deterioration of HRQOL in elderly. It was found that higher levels of CRF are related to higher level of cognitive function among healthy older adults. Moreover, aerobic fitness training enhanced the cognitive function among sedentary elderly. However, the available few studies were generally conducted in elderly individuals. Therefore, the second goal of the proposed study is to investigate whether findings from the symptom-limited maximal treadmill test duration and its change over 20 years predict cognitive function in the CARDIA study in order to better understand the pathogenesis of cognitive function impairment and HRQOL in adulthood.

Brain MRI, measuring both morphological and functional aspects of the brain, is used to study and diagnose the neurologic diseases, including dementia, Parkinson's disease, and neoplasm. White matter lesions detected by MRI have been linked with diminished cognitive functioning in elderly in a few large prospective cohort studies. Importantly, CRF was recently found to be associated with brain MRI changes in patients with multiple sclerosis and early-stage Alzheimer's disease. No prospective cohort study investigating this association in a healthy middle-aged population has been done. Therefore, the third goal of the proposed study is to evaluate whether CRF predicts brain MRI among apparently healthy middle-aged adults in the CARDIA study, which would

further help to identify whether early brain changes mediate the association of CRF with cognitive function impairment.

Health-related quality of life (HRQOL) mainly represents an individual's perceived physical and mental health and is widely used in the public health setting to evaluate health care quality. CRF is associated with HRQOL in patients with cardiovascular diseases, or after organ transplantation. Recently, CRF was found to be positively related to HRQOL in healthy elderly. However, no prospective cohort study investigating this association within apparently healthy young adults has been done so far. Therefore, it is unclear whether CRF predicts future HRQOL in healthy young adults. Thus, the first goal in this proposal is to examine the association between results of the symptom-limited maximal treadmill test duration and HRQOL in the Coronary Artery Risk Development in Adults (CARDIA) Study cohort, 5115 healthy men and women aged 18-30 at the initiation of the study.

B. Background

B.1. Cardiorespiratory Fitness and Performance Potential

B.1.1 Introduction of Cardiorespiratory Fitness

Cardiorespiratory fitness (CRF), also termed as aerobic capacity, is the ability of the body's circulatory (including heart and blood vessels) and respiratory systems to supply oxygen to skeletal muscles during sustained physical activity. CRF represents the body's oxygen-forwarding capacity of the cardiorespiratory system. CRF is considered as a health-related component of physical fitness and is often expressed in maximal oxygen uptake (VO2 max) obtained from treadmill tests. VO2max is considered as an international reference standard of cardiorespiratory fitness [1]. In healthy subjects, VO2max depends on dimensional factors and functional capacities. Dimensional factors refer to the influence of the size and capacities of the organs in the oxygen transport line, such as the maximal heart rate, and the size of the heart, lungs, diffusing surface, and the pulmonary capillary bed; while the functional capacity of the cardiovascular system refers to the maximal cardiac output and the stroke volume maintained during sustained physical activity. Generally, in normal subjects, during exhausting work, inadequate functional capacity of cardiovascular system, including inability to maintain a large stroke volume or to increase heart rate, would limit the oxygen transport capacity [2].

Recent epidemiological studies showed that CRF level is determined by both modifiable (physical activity, smoking, obesity, and health status) and non-modifiable (age, gender, and heredity) factors, with physical activity as the primarily determinant [3, 4, 5]. The

finding that functional capacity of certain organs and tissues increases in response to regularly performed exercise and decreases with lack of exercise has provided the physiologic base for the roles of exercise in CRF level and further in the preventive medicine [6]. Findings from epidemiologic studies and randomized controlled trials showed that regular physical activity or exercise is often associated with higher or improvements in CRF and this association is dose-dependent [7]; [8-10]; [11,12]. Smokers are found to have lower CRF levels compared to never smokers or former smokers [12-14].

According to the data from the 1999-2004 National Health and Nutrition Examination Survey, obese participants had approximately 10% lower CRF than normal weight participants [15]. For each 1 kg/m^2 increase in body mass index, the CRF declined by 0.20 metabolic equivalents of task (METs) in women and 0.32 METs (-0.33 to -0.20) in men [12]. Furthermore, BMI alone explained about 10% of the variance in maximal exercise duration in men taking a Bruce-protocol exercise test and 44% of the variance in maximal exercise duration in women [16,17]. Also, certain health conditions such as higher blood pressure, higher cholesterol, lower HDL, and higher glucose level have been shown to be associated with lower CRF level [13,18]. Therefore, concurrent health status is also a correlate or determinant of CRF.

In addition to modifiable factors, some non-modifiable factors, including age, gender,

and genetic factors, play an important role in the CRF. The fact that age is inversely related to maximal heart rate attained on the treadmill test demonstrated that age is a determinant of CRF [19-21]. The decline in CRF with age is non-linear and more pronounced in later adulthood [12,22]. It is worth noting that women often have lower CRF levels than men at the same age group [15,12,18]. In terms of genetic factors, studies showed that the heritability of indicators of CRF reaches about 50% of properly adjusted fitness traits [23,24]. Additionally, significant gains in fitness from regular exercise or exercise training were affected by genetic factors [25].

B.1.2 Measurements of Cardiorespiratory Fitness

CRF can be expressed in a few different measurements. Although directly measured VO2max is the most precise measurement available for CRF level, CRF is often measured as estimated metabolic equivalents (METs) in many studies due to practical issues, such as costs and time availability. METs represent the ratio of metabolic rate during an activity to a reference rate of metabolic rate at rest. For instance, 5 METs signifies that a person increases metabolic rate 5-fold during a specific activity compared to resting metabolic rate [5]. In those studies in which it is not possible to obtain directly measured VO2max or estimated METs, maximal heart rate or maximal duration till exhaustion in an exercise test could be used as CRF measurements.

While VO2max obtained from maximal treadmill tests is considered as an international reference standard of CRF [1] and is highly recommended, even where a study has the resource to perform a true maximal treadmill test, many people may fail to achieve exercise performance sufficient to directly measure the VO2max, especially among sedentary individuals unused to exercise, who may easily complain of fatigue and shortness of breath during the tests, and subjects with specific medical conditions, such as coronary heart disease or musculoskeletal and joint impairments. Under these circumstances, a submaximal exercise test can be performed by almost everyone, without restriction to those who are fittest, or free of medical conditions are in great need. Submaximal exercise tests, which take into account the medical conditions of participants, daily activity habits, and cost and duration of studies, are convenient to conduct in practice. Importantly, submaximal tests appear to be reliable and valid with correlation coefficients between measured and estimated VO2max in the range between 0.7 and 0.9 for different submaximal tests, including the modified Bruce treadmill test, Astrand and Ryhming cycle ergometer tests, 12-minute run test, 20-meter shuttle test, and 1-mile track walk test [26,27] .

Additionally, different from a submaximal test which has an upper limit set for the performance of the participants, a symptom-limited maximal test encourages participants to attempt to perform their maximal capacity without any previously set limit. The fact that participants can terminate the tests when they have any symptoms that limit their performance, including fatigue, shortness of breath, and any medical reasons make

symptom limited maximal tests more flexible than true maximal tests. With person-to-person variation, symptom-limited maximal tests may vary in the percent of maximum actually achieved by participants.

B.1.3 The Importance of Cardiorespiratory Fitness and its Change

There is convincing evidence showing that CRF is associated with morbidity and mortality independently of other risk factors. According to different cohort studies conducted in United States, Canada, Norway, Denmark, France, Finland, Japan, and Belgium, low CRF is associated with higher risk of coronary heart disease events (myocardial infarct and sudden cardiac death), cardiovascular death and all-cause mortality [28]. In addition to its protective effect on coronary heart disease, CRF is likely to be protective for other cardiovascular diseases, such as fatal and non-fatal stroke in both healthy men and women[29,30] .

It is worth noting that low fitness is an essential independent predictor of mortality. Blair and his group found that low fitness is a predictor of high mortality, independent of smoking status, cholesterol levels, blood pressure and chronic illness, and its prediction is stronger than high blood pressure and high cholesterol in 25341 men and than smoking in 7080 women [31]. Also, in the same cohort study, CRF was found to be more strongly associated with all-cause mortality than self-reported physical activity among both men and women [32]. Moreover, among men with or without an abnormal exercise test result or a history of cardiovascular disease, CRF is found to be a more powerful predictor of mortality than established risk factors such as hypertension, smoking, and diabetes. Each

1-MET increase in CRF was associated with a 12% reduction in mortality [33].

While there are substantial studies supporting that low CRF is a strong risk factor for cardiovascular disease and total mortality, studies from several longitudinal cohort studies further showed that high CRF is associated with low risk of developing cardiovascular disease risk factors. Results from the Coronary Artery Risk Development in Adults (CARDIA) Study demonstrate that among 5115 initially healthy men and women, after 15 years of follow-up, individuals with low CRF levels have higher risk of developing incident type 2 diabetes, hypertension, the metabolic syndrome (defined according to National Cholesterol Education Program Adult Treatment Panel III), hypercholesterolemia, and coronary artery calcification[14,13,34]. According to the findings in the Aerobics Center Longitudinal Study (ACLS), a prospective epidemiological study of about 20,000 men aged 20–85 years followed from 1970 through 2003, men with lower CRF tended to have higher risk of type 2 diabetes, hypertension and the metabolic syndrome [35,36]. Moreover, low CRF is shown to be related to a decreased insulin sensitivity compensated by higher insulin secretion in both African-American and white youth, overweight and obese postmenopausal women, and subjects who are at risk of insulin resistance syndrome and type 2 diabetes [37-39]. In the Aerobics Center Longitudinal Study (ACLS), CRF was found to be inversely associated with several inflammation markers, including C-reactive protein, plasma fibrinogen, and white blood cell count[36,40,41]; while in the National Health and Nutrition Examination Survey 1999-

2002, CRF was found to be associated with C-reactive protein [41]. Among women with polycystic ovary syndrome, CRF was independently and inversely associated with common inflammation markers [42]. In patients with type 2 diabetes, CRF was found to be associated with a fibrinolytic factor, tissue plasminogen activator (t-PA) antigen [43], although no independent association between CRF and markers of thrombosis were found in healthy middle-aged men and women [44]. The associations between CRF and these cardiovascular disease risk factors helped to illustrate the potential mechanisms underlying its associations with cardiovascular disease and total mortality.

Since CRF level may change due to changes in modifiable determinants, especially physical activity behavior and weight over time [17,45], it is worth investigating whether changes of CRF levels are also associated with morbidity and mortality. In the CARDIA study, decreased CRF over 7 years was associated with decreased HDL, increased LDL, total cholesterol, triglycerides and risk of developing diabetes [46,47]; subjects who developed diabetes over 20 years had significant decreases in fitness over 20 years compared to those who did not develop diabetes over the follow-up [47]. In the ACLS study, men who were unfit at two examinations about 4.9 years apart had the highest mortality, those who changed fitness status had intermediate mortality, and those who were fit at both visits had the lowest mortality [48]. In another study of healthy Caucasian

middle-aged men, changes in fitness over 7 years significantly predicted overall mortality with the improvements associated with a considerably reduced mortality [49].

Given the fact that CRF is a strong predictor of cardiovascular risk factors, cardiovascular disease and all-cause mortality, and can be modified by physical exercise, CRF has the potential to play an important role in the prevention and improvement of these medical conditions. Moreover, unlike physical activity which is often collected as a self-reported variable, CRF is measured objectively by exercise tests, such as maximal or submaximal treadmill tests, and would therefore provide a more precise measurement of the body fitness level and would be more helpful in classifying individuals' risk for future medical conditions. Also, in addition to being closely related to one's physical activity habit, which may be mainly influenced by one's motivation, CRF captures the physiologic capacity of the body's cardiopulmonary system to perform exercise, which makes it an important tool to understand the pathophysiology of certain cardiovascular and cerebral diseases. Therefore, CRF is an ideal exposure variable to assess when studying risk of certain disease or health condition.

B.1.4 Maximal Treadmill Duration – Measure of Cardiorespiratory Fitness and Treadmill Performance Potential

Maximal treadmill duration (Max_{dur}) of a symptom-limited treadmill test is widely used as a close approximation of VO_2max obtained from a maximal treadmill test to measure CRF (r=0.92) [27]. However, as treadmill duration is influenced by multiple aspects of both

physiologic and psychologic functioning, Max_{dur} could be considered more as a measure of the treadmill performance potential of the tested human being, rather than simply the capability of a particular organ or system, particularly the cardiorespiratory system[50,17]. Obesity is a good example to address this issue. It is very likely that obese participants do not perform as close to their true maximum on a symptom-limited maximal treadmill test as do leaner people, because they are not accustomed to exercise or to sweating and exercise-induced fatigue; for the same reason, obese people may decline to even perform a true maximal treadmill test, in which they would be asked to continue performing into their maximal heart rate plateau. As obesity is linked with a high risk of degenerative joint diseases [51], obese participants tend to suffer more from joint problems which may interfere with treadmill performance. Clearly, neither one's previous experiences with exercise and physical exertion, nor joint problems represent the function of one's cardiorespiratory system, therefore one's treadmill duration would capture one's performance as a whole rather than just cardiorespiratory fitness[50].

B.2. Cognitive Function and its Association with Cardiorespiratory Fitness

Cognition function refers to mental processes including verbal learning and memory, sustained attention, concentration, visuomotor coordination, motor function, and the ability to understand language, to solve problems, and to make decisions. Cognitive function declines with aging [52]. In 2009, 11% of the world population were older than 60 years old (21% in more developed regions, 8% in less developed regions, and 5% in least developed regions). With social, economic and health care development, it is expected

that in 2050, there will be 22% of the total world population older than 60 years of age (33% in more developed regions, 20% in less developed regions, and 11% in least developed regions)[53]. Therefore, the prevalence of cognitive function impairment will continually increase worldwide. Mild cognitive impairment is the stage between normal forgetfulness due to aging and the development of dementia, a loss of brain function affecting memory, thinking, language, judgment, and behavior. Though not everyone with mild cognitive impairment develops dementia, it is still an important precursor for the development of dementia. Most types of dementia are nonreversible and degenerative. Among all different type of dementias, Alzheimer's disease is the most common type of dementia followed by vascular dementia [54]. By 2030 the number of Americans diagnosed with dementia is expected to more than double to 5.2 million [55]. Among dementia patients older than 60, the prevalence and incidence rates of depression were higher than those without dementia. In addition to its association with dementia, cognitive function impairment is also linked with high risk of stroke [56].Cognitive impairment is one of the main threats to independence in elderly with impaired cognitive function, which increased the risk of being limited in daily activities [57].

Therefore, understanding the factors that contribute to impaired cognitive function is an important public health issue to help prevent development of diseases, such as dementia and stroke, and limitation of daily activities in the general population. Identification of factors related to preservation of cognitive function and risk factors related to cognitive function impairment is undoubtedly helpful in improving the HRQOL in elderly.

Many factors are associated with the development of impaired cognitive function. Studies

showed that people with type 2 diabetes mellitus have a higher risk of dementia and cognitive function impairment which might be mediated by chronic hyperglycemia and increased vulnerability to recurrent hypoglycemia [58]. Hypertension was found to be associated with increased risk of impaired cognitive function, especially decreased performance in executive function and attention tests [59]. Also, it is found that patients with peripheral arterial diseases are prone to develop impairment of cognitive function[60] .

CRF predicts cardiovascular diseases including stroke and overall mortality [30,13,29,31,47,61, 28]. Recent studies showed that CRF is positively related to cognitive function among healthy older adults while aerobic fitness training improves the cognitive function among healthy but sedentary older adults and those with mild cognitive impairment [62-64]. Results from several randomized controlled trials found that an exercise regimen of 6 weeks and at least 3 times per week for 60 minutes would improve cognitive function in the healthy elderly or impaired cognitive function [65]. However, these studies were limited to older individuals. No longitudinal investigations have been conducted to investigate the relation between CRF and cognitive function in healthy young and middle-aged adults.

Among patients with multiple sclerosis, it was found that higher level of CRF is positively related to white matter integrity, which suggests complex associations between CRF, preserved white matter structures, and cognitive function [66].

The evidence for the association between CRF and cognitive function is scarce and mostly limited to elderly individuals. Whether white matter lesions mediate this association is unclear. Therefore, investigating this association among apparently healthy

middle-aged adults of the CARDIA study would be useful and would allow us to gain a better understanding of the pathogenesis of cognitive function impairment in adulthood.

B.3 Brain MRI and its Association with Cardiorespiratory Fitness

Brain MRI, which measures both morphological and functional changes in the brain, is often used in understanding and diagnosing the neurologic diseases, including dementia (e.g., Alzheimer's disease, and vascular dementia), movement disorders (eg, Parkinson's disease), mass lesion (e.g., neoplasm), and/or focal neurologic deficit (infarction and intracerebral hematoma). Alzheimer's disease is usually associated with enlarged cerebrospinal fluid spaces, abnormal signal intensity in medial temporal lobe, and cortical atrophy in brain MRI. Generalized brain atrophy and iron accumulation in pars compacta of the substantia nigra are the frequent findings for those with Parkinson's disease [67]. Also, white matter hyperintensities are often related to Alzheimer's disease, vascular dementia, hypertension, cerebral small-vessel disease, and normal aging [68-73]. In several large population studies of middle-aged and elderly individuals, such as the Cardiovascular Health Study, the Atherosclerosis Risk in Communities Study, the Framingham Offspring Study, and the Rotterdam Study, white matter lesions are found to be related to or even predict diminished cognitive functioning in elderly individuals [74-77].

In addition to the pathologic findings, brain MRI can capture normal changes with aging, such as enlargement of the ventricles, hyperintensity in the white matter and basal ganglia, arteriosclerosis in large and small arteries, amyloid angiopathy in leptomeningeal

vessels[68]. Therefore, brain MRI is an ideal measurement to capture some potential structural changes before clinical onset of certain neurological diseases among generally healthy population, which would thus be beneficial in learning the pathophysiologic mechanism and potential risk factors of neurologic diseases in the early disease process.

CRF is known to be a predictor of cardiovascular diseases and overall mortality [13,29-31,47,61,28]. Recent studies showed that CRF was associated with brain MRI changes in some diseased populations. Among patients with multiple sclerosis, it was found that CRF level is positively related to white matter integrity, regional gray matter volumes, and higher focal fractional anisotropy values [78]. In early-stage Alzheimer's disease, increased CRF was associated with reduced brain atrophy (higher whole brain volume, regional brain volume in the medial temporal and parietal cortice, and white matter volume) [79-81]. In a study of 86 older adults (mean age of 65 years old, 45% hypertensive, and 36% hyperlipidemic), CRF was found to be significantly correlated with hippocampus volume [82].

To date, the evidence for the association between CRF and brain MRI findings is mostly limited to diseased persons or elderly individuals. No longitudinal study investigating the association of CRF and brain MRI changes in apparently healthy adults has been done. Therefore, investigating this association among apparently healthy middle-aged adults such as the cohort of CARDIA study would be crucial with the aim of identifying potential risk factor for early brain structural changes in healthy population and thus finding a way to prevent brain structural changes which may lead to certain degenerative neurological diseases.

B.4. Quality of Life and its Association with Cardiorespiratory Fitness

Health-related quality of life (HRQOL) is a broad multidimensional concept defined by The World Health Organization (WHO) as "an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns". It depends on an individual's physical health, mental state, level of independence, social relationships, and their relationship to the environment [83-85] HRQOL mainly represents an individual's perceived physical and mental health and is widely used in the public health setting to evaluate health care delivery, to eliminate health care disparities, and to predict future medical health care costs [84-86]. In clinical medicine, HRQOL is an important measurement to assess the impact of various health conditions, to evaluate the benefits of healthcare, and to examine the effect of target therapeutic interventions. It is well known that an individual's HRQOL would be impaired to some extent by different diseases and their complications and comorbidities, such as congenital diseases (cystic fibrosis), joint diseases (rheumatic arthritis and osteoarthritis), general injury, Parkinson's disease, chronic diseases (celiac disease, hypertension, diabetes, kidney disease), cancer (kidney cancer, hepatocellular carcinoma, and leukemia), etc. [87-93]. Appropriate interventions have been found to improve HRQOL among patients with symptomatic or asymptomatic diseases[89,92,94,95].

Physical activity is consistently positively associated with HRQOL in cross-sectional studies in the general adult population; while limited evidence of this association was found in cohort studies and randomized clinical trials. As a result, a final statement of this association could not be made currently [96]. Identification of a positive association

between PA level and HRQOL in the general population is very important from the public health point of view, because it will motivate healthy adults to become more physically active with the purpose of maintaining or improving HRQOL later in their lives. Also, finding a positive association of physical activity with HRQOL would help to identify high-risk individuals in advance and would thus prevent the deterioration of their HRQOL later in life. However, as physical activity is often collected in a self-reported format, CRF, which is objectively measured through exercise testing and is primarily determined by one's physical activity levels, would probably provide a more precise measurement of the body's fitness level and would be more helpful in classifying individuals' risks and targeting high-risk persons.

CRF is an important predictor of cardiovascular disease and overall mortality [13,29-31,47, 61,28]. Previous studies showed that CRF is associated with HRQOL in certain diseased populations, such as patients with mild hypertension, diabetes, or coronary heart diasease, or patients after cardiac rehabilitation, bariatric surgery, or organ transplantation [97-101]. Moreover, recent cross-sectional studies showed that higher CRF was associated with higher level of HRQOL even in apparently healthy participants [97,102-104]. However, these studies were limited to older individuals, fit young men in the US Navy, or had small sample size. Therefore, their results could not be generalized to the general population. Also, the cross-sectional nature of these studies makes it impossible to assess temporal associations of the variables, which is an important constituent of inferring a direct causal relationship between CRF and HRQOL from these studies. Hence, despite these findings, longitudinal cohort study which would investigate whether higher CRF predicts better

HRQOL years later in apparently healthy young adults are greatly needed in order to further explore the association of CRF with HRQOL.

C. Study Designs and Methods

C.1. Description of Coronary Artery Risk Development in Adults (CARDIA) Study

The CARDIA Study is a multi-center longitudinal cohort study of cardiovascular risk factors in 5115 men and women between the ages of 18 and 30 years at study inception in 1985-1986. There are four clinical study centers, Birmingham, AL, Chicago, IL, and Minneapolis, MN, and Oakland, CA. Recruitment was at random from the general population in Birmingham, AL, Chicago, IL, and Minneapolis, MN, and from members of the Kaiser Permanente Medical Care Plan in Oakland, CA. Contact letters with detailed purpose and specifics of the study was sent to the designated potential participants initially, followed by telephone interviews 2 weeks later. Oakland, Chicago and Birmingham used only telephone recruitment, while the Minneapolis center used both telephone interview and door-to-door visits for recruitment. Approximately 50% of those who were invited to the study finally participated in the CARDIA study.

The full CARDIA Study sample at baseline was balanced by age (45% aged 18-24 years; 55% aged 25-30 years), race (52% African American; 48% white), sex (46% men; 54%, women), and educational achievement (40% completed ≤12 years; 60% >12 years) [105-107]. Each center had a heterogeneous and balanced study sample. Overall, eligible CARDIA study participants were between 18 and 30 years old at the study inception, of black or white race, in good overall health, and able to walk on a treadmill, and had a permanent address in the designated area. Subjects, who were chronically ill, disabled, institutionalized, pregnant, or within 3 months of delivery, were not eligible for the CARDIA study.

Seven follow-up examinations were conducted during 1987-1988 (Year 2), 1990-1991 (Year 5), 1992-1993 (Year 7), 1995-1996 (Year 10), 2000-2001 (Year 15), 2005-2006 (Year 20), and 2010-2011 (Year 25), with 91% (n=4624), 85% (n=4352), 80% (n=4086), 79% (n=3950), 74%(n=3672), 72% (n=3549), and 72% (n=3499) of the surviving cohort returning, respectively . For the purpose of the proposed study, men and women in whom the symptom-limited treadmill exercise tests were performed at year 0, 7, and 20 (the last as part of the ancillary CARDIA Fitness Study, Stephen Sidney, PI) will be included in the subsequent analysis.

C.2. Data Collection

C.2.1 Overall data collection

Data were collected on a variety of cardiovascular risk factors, including sociodemographic (age, race, gender, education), behavioral (dietary habits, physical activity, smoking status, drinking habits), physiologic (weight, height, body mass index, adiposity, lung function), and clinical biological variables (insulin, glucose, adiponectin (the last obtained as part of the YALTA ancillary study to CARDIA), etc.). Subclinical cardiovascular outcome (coronary artery calcification, carotid artery wall thickness, and other echocardiography variables) and clinical cardiovascular outcomes (hypertension, hyperlipidemia, diabetes, obesity, chronic kidney disease, and the metabolic syndrome) were also collected throughout the 25 years of follow-up. Extensive quality control was conducted in CARDIA through all data collection processes.

C.2.2 Graded Treadmill Exercise Test

The graded symptom-limited maximal exercise test followed a modified Balke protocol, which consisted of up to nine 2-minute stages of gradually increasing difficulty. Stage 1 was 2% grade at 3 miles per hour, stages 2-6 were 6, 10, 14, 18, and 22% grade at 3.4 miles per hour, stages 7 and 8 were 22 and 25% grade at 4.2 miles per hour, and stage 9 was 25% grade at 5.6 miles per hour. [108]. Participants were determined to be ineligible for the test because of history of heart disease, abnormal ECG, elevated resting blood pressure, and acute illness with a fever (the last if it was infeasible to reschedule for a later date [22]. For those who were eligible for the tests, about 98% of participants at all years ended the tests due to shortness of breath or fatigue.

Max_{dur} representing the duration of the symptom-limited treadmill test was calculated at the end of the test. Heart rate (beats/minute) was measured by ECG at the end of each stage and upon cessation of the test. Rating of perceived exertion (RPE) using a 15 point Borg scale (range 6-20) was asked at each stage[109].

The symptom-limited treadmill test was performed by 4969, 3560, and 2871 participants (97%, 70%, and 56% of the CARDIA cohort) at years 0, 7, and 20, respectively. A systematic protocol violation of the year 7 tests was discovered in the Minnesota clinic after the examination period ended [110]. Participants who took the tests in the Minnesota clinic (n=977) at year 7 tended to have longer Maxdur (711.8 seconds versus 545.7 seconds) with lower maximum heart rate (174.4 beats/minute versus 177.9 beats/minute) than those who took tests at other clinics (n=2583) at year 7 examination. In terms of baseline characteristics, these participants were more likely to be current smokers (36% versus 25%), and had lower maximal treadmill test duration (583.4 seconds versus 600.8

seconds), than people took tests at other clinics at year 7 [22]. For main analysis, these 977 tests were not included. Strongly imputed maximal duration of these 977 tests in Minneapolis center (multiple correlation coefficients about 0.9 based on better measured correlates among those without missing data in the remaining clinics) will be included in the sensitivity analyses. For the current study, we further excluded 177 tests of participants with concurrent beta blocker medication use (34, 4, and 139 tests at year 0, 7 and 20, respectively, because beta blockers uncouple the exercise heart rate and the duration on treadmill, thereby changing the meaning of both submaximal and maximal durations) and 534 tests that were terminated for medical reasons including abnormal ECG manifestations, abnormal blood pressure changes, and several other medical reasons such as back pain, nausea or dizziness (299, 199, and 36 tests at year 0, 7 and 20, respectively, because duration in such tests would not necessarily reflect exercise performance potential). We also excluded all 109 tests of participants who were younger than 18 or older than 30 years of age at the time of baseline testing (56, 26, and 27 tests at year 0, 7 and 20, respectively, because several of our analyses focused on age, and these few people were not felt to be sufficient to reflect their age category). Some participants met more than one exclusion criteria. This leaves 4590, 2356, and 2677 tests at year 0, year 7, and year 20, respectively. Most of the analyses in the present study were conducted in these 9623 tests in 4844 participants, with sensitivity analyses adding 977 tests at year 7 in MN.

C.2.3 Measurements of Covariates

Sociodemographic variables, including age, race, sex, education levels, cigarette smoking,

dieting behavior, and alcohol use were obtained by self- and interviewer-administered questionnaires at each clinic visit [111-113]. Physical activity level was measured at each examination by a separate interviewer-based questionnaire regarding the frequency of 13 different activities during the past 12 months; the activity level was estimated by "Exercise Units" (EU) [114,115]. Hours per week of TV viewing was assessed by the answers to questions about frequency and duration of watching [116].

Body weight was measured using a balance beam scale and height using a vertically mounted metal centimeter ruler and a metal carpenter's square. Body mass index (BMI) was derived from the formula: weight(kg) / height(m)^2. Seated blood pressure was measured three times after 5 minutes of rest with the average of the last two measurements used in analysis. Concurrent use of β-blocker medications was also obtained from self reports, with examination of medication bottles when available, at each time period. Lung function was measured at years 0, 2, 5, 10, and 20 using a volume-based spirometer (SensorMedics, Inc., Yorba Linda, CA) and following the standard procedures of the combined American Thoracic Society and the European Thoracic Society guidelines [117-119].

Standard procedures were used to draw blood at each center and process the blood sample sample at the central laboratory. Before each examination, participants were asked to avoid smoking and heavy physical activity for at least 2 hours and stay fasting for at least 8 hours. Glucose was measured using the hexokinase method. Total cholesterol and triglycerides were assayed by enzymatic methods. High-density lipoprotein (HDL) cholesterol was measured after dextran sulfate-magnesium

precipitation [105]. LDL cholesterol was estimated with the Friedewald equation [120]. All laboratory assessments were performed without knowledge of other data.

C.3. Human subjects

The institutional review boards for the protection of human subjects for the participating study sites provided approval for the study, and written informed consent was obtained from all participants at the baseline and each follow-up examination. The consent forms stated the purpose of the study, study process, risks and benefits of participation in the study, and confidentiality in details. At follow-up examinations, if new measurements were added, for instance genotyping using DNA, echocardiography, cognitive function tests, or brain MRI, informed consent was obtained. Participants possessed the right to refuse to participate in the study at any time.

The potential risks of participating in the study included possible discomfort or bruising from the blood draws, shortness of breath or fatigue from treadmill exercise test, and minimal radiation exposure from the dual energy x-ray absorptiometry (DEXA) scan and the computed tomography, or claustrophobic reaction to the brain MRI. The benefits of participating in the CARDIA study included free comprehensive medical exams at the examinations, and notification of the primary care physicians about any abnormal exam results for consented participants.

The data released to data analysts are de-identified and referenced by study ID to protect the confidentiality of the participants. Only approved study personnel have access to study records with identifiers. Data are disclosed only to study investigators except in

some situations, if the participant requested or consented, the data could be disclosed to those who are not involved in the study, such as abnormal exam results were released to the primary care physician of a participant.

D. Manuscript 1 - Cardiorespiratory Fitness and Cognitive function in Middle-Age: The CARDIA Study

D.1. Introduction

Cognitive function is commonly considered to include verbal learning and memory, sustained attention, concentration, visuomotor coordination, motor function, and the ability to understand language, to solve problems, and to make decisions. Cognitive function declines with aging [52]. In 2009, 11% of the world's population was over 60 years old. With social, economic and health care development, it is expected that in 2050, 22% of the total world population will be older than 60 years of age [53]. As a result, the prevalence of cognitive function impairment is likely to increase continually worldwide.

Therefore, understanding the factors that contribute to preservation of cognitive function throughout adulthood is an important public health issue that could lead to prevention of some diseases and reduce limitation of daily activities in the general population. Cardiorespiratory fitness (CRF), measured by treadmill duration, is closely related to cardiovascular diseases and overall mortality [30,13,29,31,47, 61,28]. Since CRF level may change due to changes in modifiable determinants, especially physical activity behavior and weight over time [17,45], CRF is a potential factor that could be intervened on to prevent cognitive function decline in the general population. Recent studies showed a positive association between CRF and cognitive function. In a community-based study of healthy participants older than 55 year old, lower baseline CRF was associated with greater decline over 6 years on a modified Mini-Mental State Examination, a generally used test

for cognitive function in the elderly. Higher baseline CRF was further found to be related to better performance on cognitive tests measuring attention, executive function, verbal memory and verbal fluency 6 years later in the same study [63]. In a meta-analysis of 18 studies, CRF improvement through training was associated with better cognitive function including executive, controlled, spatial and speed function among healthy adults aged 55 and older or those with mild mental disorders and cardiopulmonary obstructive [62]. In addition, lower CRF was related to progression of dementia severity in Alzheimer's disease [81]. Estimated CRF, calculated from an equation based on age, sex, body mass index, resting heart rate, and self-reported physical activity level, was found to relate to processing speed, spatial working memory, and memory complaints [82]. However, current evidence for the association between CRF and cognitive function is scarce outside of studies in elderly individuals.

By age 55 years, pathophysiologic changes underlying both loss of CRF and loss of cognitive function may already have occurred[13,17,22,121]. No longitudinal studies have been conducted to investigate the relation between CRF and cognitive function in healthy young and middle-aged adults, when the treadmill duration is likely to be as high as it will be in the lifetime. Therefore, investigating the association between CRF and cognitive function among apparently healthy middle-aged adults of the Coronary Artery Risk Development in Young Adults (CARDIA) study would be useful and would allow us to gain a better understanding of the pathogenesis of cognitive function in adulthood. We hypothesize that baseline CRF, defined by symptom-limited maximal treadmill test duration (Max_{dur}) and its change over 20 years are associated with cognitive function in

midlife.

D.2. Methods

D.2.1.Study design

CARDIA is a multi-center longitudinal cohort study of cardiovascular risk factors in adults between the ages of 18 and 30 years at study inception in 1985-1986. Recruitment was at random from the general population in Birmingham, AL, Chicago, IL, and Minneapolis, MN, and from members of the Kaiser Permanente Medical Care Plan in Oakland, CA. The full CARDIA sample at baseline was balanced by age (45% aged 18-24 years; 55% aged 25-30 years), race (52% black; 48% white), sex (46% men; 54%, women), and educational achievement (40% completed ≤12 years; 60% >12 years) [107,105,106]. Seven follow-up examinations were conducted at years 2, 5, 7, 10, 15, 20 and 25, with 91%, 86%, 81%, 79%, 74%, 72% and 72% of the surviving cohort returning, respectively. Our analysis includes men and women who did symptom-limited treadmill exercise tests at year 0 and cognitive testing at year 25. In addition, we studied the subset who also did the treadmill test at year 20 as part of the ancillary CARDIA Fitness Study. The institutional review boards for the protection of human subjects for the participating study sites provided approval for the study, and written informed consent was obtained from all participants.

D.2.2. Data collection

Graded exercise testing

The graded symptom-limited maximal exercise test followed a modified Balke

protocol, consisting of nine 2-minute stages of gradually increasing difficulty [108]. Stage 1 was 2% grade at 3 miles per hour, stages 2-6 were 6, 10, 14, 18, and 22% grade at 3.4 miles per hour, stages 7 and 8 were 22 and 25% grade at 4.2 miles per hour, and stage 9 was 25% grade at 5.6 miles per hour. Maximal duration of symptom-limited exercise on a treadmill (Max_{dur}) was the primary exposure. Max_{dur} is a close approximation of cardiovascular fitness and of the true physiological maximum oxygen consumption per unit time (VO_2max) on a treadmill [27]; nevertheless, functioning of other body systems also plays a prominent role in Max_{dur} because of the volitional symptom-limitation as the stopping criteria. Max_{dur} can be seen as a measure of treadmill performance potential in the face of the maximal physical exertion that the individual can tolerate. Participants (n=128 at year 0 and 127 at year 20) were determined to be ineligible for the treadmill test for the following reasons: history of ischemic heart disease, use of cardiovascular medications (except high blood pressure medication), elevated resting blood pressure (systolic blood pressure>160 mmHg or diastolic blood pressure>100 mmHg), or acute illness with a fever (test was rescheduled for a later date whenever possible)[22]. Criteria for terminating the exercise test included general or leg fatigue, shortness of breath, or participant refusal to continue, and certain medical reasons**.**

Cognitive function assessment

At the year 25 examination, a battery of three standardized tests was conducted to measure cognitive function. 1) The Rey Auditory Verbal Learning Test (RAVLT) assesses memory, including the ability to memorize and to retrieve words (verbal memory)[122]. Results from the long delay (10 min) free recall were used in analyses. The

range of number of words recalled is 0 to 15, with higher number indicating better performance. 2) The Digit Symbol Substitution Test (DSST) mainly assesses processing speed. It evaluates visual motor speed, sustained attention, and working memory[123]. The range of digits correctly substituted by symbols is 0 to 133, with higher number indicating better performance. 3) The Stroop Test evaluates executive function, including the ability to view complex visual stimuli and to respond to one stimulus dimension while suppressing the response to another dimension[124]. The test was scored by the time (seconds) to correctly state color of the words printed in ink with different color plus number of errors, thus, a higher score indicates worse performance on the task.

Measurements of other variables

Sociodemographic variables, including age, race, sex, education level, cigarette smoking, diet behavior, and alcohol use were obtained by self- and interviewer-administered questionnaires at each clinic visit [111-113] Physical activity level was measured at each examination by a separate interviewer-based questionnaire regarding the frequency of 13 different activities during the past 12 months; the activity level was estimated by "Exercise Units" (EU) [114,115]. Frequency and duration of TV watching was also assessed [116]. Body weight was measured using a balance beam scale and height using a vertically mounted metal centimeter ruler and a metal carpenter's square. Body mass index (BMI) was derived from the formula: weight(kg) / height(m)^2. Seated blood pressure was measured three times after 5 minutes of rest with the average of the last two measurements used in analysis. Concurrent use of β-blocker medications was also obtained from self reports, with examination of medication bottles when available, at

each time period. Lung function was measured at year 20 using a volume-based spirometer (SensorMedics, Inc., Yorba Linda, CA) and following the standard procedures of the combined American Thoracic Society and the European Thoracic Society guidelines [117,125]. Blood glucose and total cholesterol were measured by standard procedures and glomerular filtration rate was estimated with the MDRD equation [105]. Diabetes was determined based on a combination of measured fasting glucose level ≥126 mg/dL, self-report of oral hypoglycemic medications or insulin, or a 2-h postload glucose ≥200 mg/dL [47]

D.2.3. Analytic Sample and Exclusion Criteria

The exercise test was performed by 4969 and 2871 participants at year 0 and year 20 across all CARDIA clinics, respectively. For the main analysis of the year 0 Max_{dur} (minutes), we excluded 34 tests of participants with concurrent beta blocker medication use and 299 tests that were terminated for medical reasons because the treadmill test was stopped for a priori safety reasons if a medical condition was encountered. Some participants met more than one exclusion criteria, leaving 4638 treadmill tests for data analysis. Of these 4638 participants, 3033 completed year 25 cognitive function tests were initially considered for the analysis. 289 tests with missing covariates were further excluded. Therefore, 2744 participants were included for the current study analysis for the association between year 0 Max_{dur} and cognitive function. The excluded were more likely than those included to be black, to be smokers, and to have lower educational attainment, although all of those groups were well represented among those included.1955 participants out of the 2744 participants with both eligible year 0 and year

20 treadmill tests were included in the analysis involving change of Max_{dur} over 20 years. As we previously noted [22], poor treadmill performance at baseline predicted failure to perform the test at year 20. Thus, although CARDIA tested a broad range of people at year 20, the year 20 sample is biased towards people with somewhat better fitness as evidence by a higher baseline Max_{dur} in participants who attended both year 0 and year 20 tests (N=1955) compared to those only attended year 0 tests (N=789) (10.2(2.8) min vs 9.5(2.9) min, P<0.0001). Overall, participants who attended both year 0 and year 20 treadmill tests were slightly healthier in terms of lifestyle, weight, blood pressure, and kidney function at year 0 than those who attended only year 0 treadmill tests (data not shown).

D.2.4. Statistical Analysis

Assumptions of normality of fitness, cognitive function measurements, and covariates were checked. Baseline characteristics and means of year 25 cognitive function tests were examined across race-sex specific quartiles of Max_{dur}. T tests and chi-square tests were used to compare the differences in the means and percents between groups. Multiple linear regression models were applied to assess the associations of baseline Max_{dur} and change of Max_{dur} over 20 years with cognitive function at year 25. Baseline Max_{dur} was analyzed as a continuous variable as well as in race-sex specific quartiles, and linearity was tested for these associations. Three models were tested subsequently to account for potential confounding. Age, gender, race, education, and clinical center were adjusted in minimally adjusted models; diet, physical activity, smoking, drinking, BMI, and lung function were further adjusted in moderately adjusted models; while blood pressure,

cholesterol, diabetes status, and glomerular filtration rate were additionally adjusted in fully adjusted models. However, blood pressure, cholesterol, diabetes status, and glomerular filtration rate may be on a causal pathway that might link cognitive function with Max_{dur}, so adjustment for them might represent explanation of the mechanism of association. Sensitivity analysis of the year 0 treadmill test was conducted by replacing missing covariates with the corresponding value at a later exam or race-sex specific means (thus in n=3033). Interactions between year 0 Max_{dur} and race, sex, and education level on cognitive function tests were tested.

All statistical testing was performed using two-sided tests with the significance level of type I error (α) set at 0.05. Statistical analyses were performed using the SAS 9.2 (SAS Institute Inc., Cary, NC) statistical software packages.

D.3. Results

At baseline, the average age of the cohort was 25 years old, with 45% blacks and 56% women. Baseline Max_{dur} was significantly different across race-sex groups ($P<0.001$). Max_{dur} was 10.0(2.8) minutes for all participants at year 0; -11.3(2.1) for black men, 7.3(1.9)for black women,12.4(2.1) for white men, and 9.5(2.1) for white women.. The decrease of Max_{dur} over 20 years was 2.9(2.0) minutes for the 1955 participants, 3.6(2.1) for black men, 2.5(1.8) for black women, 3.1(1.8) for white men, and 2.5(1.8) for white women($P<0.001$). Specifically, significant differences in baseline characteristics were observed across race-sex specific quartiles of baseline Max_{dur}. Those who were more fit were more likely to be better educated, thin, nonsmoker, physically active, and

normotensive. They watched less TV, had a higher quality diet and a lower total cholesterol (Table 1).At year 25, mean words correctly recalled after long delay were 8.4(3.2) words. 70.7(15.6) digits were correctly substituted in DSST, while 44.0(12.3) seconds + errors was the score for correctly naming colors in Stroop test 3 (Table 2).

For each additional minute attained on the treadmill at year 0, there were 0.12 (SE=0.03, P<0.0001) more words correctly recalled 10 minutes after 5 presentations of a list of 15 words in RAVLT, 0.92 (SE=0.13, P<0.0001) more digits correctly substituted in DSST, and 0.52 (SE=0.11, P<0.0001) fewer seconds + errors during the Stroop Test, after accounting for race, sex, age, attained education level at baseline, and clinical center(Table 3). The difference in this model between the 4^{th} quartile and 1^{st} quartile of Max_{dur} corresponds to 21%, 34%, and 25% of the sample SD of the test score in the RAVLT, DSST, and Stroop test, respectively (Figure 1). Further adjustment for dietary pattern, physical activity, smoking, BMI, alcohol consumption, and lung function attenuated the associations slightly. Additional adjustment for blood pressure, cholesterol, diabetes status, and glomerular filtration rate yielded similar trend for each of these cognitive function tests and maintained statistical significance for the RAVLT and DSST(Table 3 & Figure 1). Sensitivity analysis of the year 0 treadmill test with missing covariates replaced by the corresponding value at a later exam or race-sex specific means (thus in n=3033) yielded similar findings (data not shown). No significant interactions were identified between year 0 Max_{dur} and race, sex, or education level on cognitive function tests (all P>0.05 with df=1 for Max_{dur} -race and Max_{dur} -sex interactions and df=2 for Max_{dur} –education interaction).

Different models including year 0 Max_{dur} alone and year 20 Max_{dur} alone were further assessed among the 1955 participants with both treadmill tests available (Table 3) . The RAVLT was better predicted by Max_{dur} at year 0 (25 years earlier) than Max_{dur} at year 20 (5 years earlier) as evidenced by a relatively smaller effect size with year 20 Max_{dur} (0.12 vs 0.10 in minimally adjusted model); while DSST and Stroop tests were better predicted by Max_{dur} 5 years earlier than Max_{dur} 25 years earlier (1.13 vs 0.87 for DSST and -0.46 vs -0.38 for the Stroop test in the minimally adjusted model) (Table 3). Of the 1955 participants who also completed the year 20 treadmill test, 1793 particpants decreased Max_{dur} over 20 years (8.2% had a longer Max_{dur} at year 20 than at year 0). The change of Max_{dur} over 20 years was positively associated with number of digits correctly substituted in 2 minutes DSST at year 25. For each additional minute lost on the treadmill over 20 years, there were 0.97 (SE=0.17, P<0.0001) fewer digits correctly substituted in DSST, with adjustment for year 0 Max_{dur}, race, sex, age, attained education level at baseline, and clinical center. Further adjustment retained the significant association for DSST. No significant associations were observed between the change of Max_{dur} over 20 years and the performance for RAVLT and Stroop test.

D.4. Discussion

In the current study, higher CRF measured by Max_{dur} at average age 25 was positively associated with better performance in cognitive function tests, including RAVLT and DSST assessed 25 years later, but not Stroop. The smaller decrease (or improvement in 143 out of 1955 participants) of CRF over 20 years was associated with better DSST performance. Our findings further confirm that the previously detected association of

CRF with cognitive function in older adults also holds for CRF assessed in young adulthood and cognitive function in middle-aged adults. In addition, it is shown for the DSST (processing speed) and Stroop test (executive function) that the closer in time the treadmill test is to the cognitive tests, the stronger the predictive value of the Max_{dur} on cognitive function test results. However, the magnitude of association with the RAVLT test of memory was greater for the earlier measure of CRF.

Our findings of significant association between change in Max_{dur} with DSST accord with previous findings of a meta-analysis of 18 studies in elder participants showing that fitness improvement after months of exercise training was associated with both processing speed and all types of cognitive function [62]. Specifically, one study conducted among 33 elderly participants with mild cognitive function impairment after 6-months of a controlled exercise intervention showed that increasing VO2 peak, a measure of CRF, was associated with improved performance in DSST specifically in the 17 female participants [64] . While the cognitive tests were measured directly after several months' of aerobic exercise intervention in the latter trial, the change in CRF observed in our study were registered over 20 years in free-living individuals and 5 years before the measurements of RAVLT, DSST, and Stroop tests; this design difference could have attenuated the putative positive fitness effect on memory and executive function. Another consideration is that memory, processing speed and executive function, may not be equally robust as people age. However, future study with measurement of baseline cognitive function in middle-aged populations is needed to clarify the effect of change in CRF on cognition in this population.

The observed association between CRF and cognitive function may have multiple mechanisms. One possible mechanism is that low CRF leads to morphological brain changes, including white matter lesions [126, 78, 79,80], and brain atrophy in certain regions in grey matter[81], which in turn related to impaired cognitive function in elderly [74-77]. On the other hand, CRF may alter cognitive function through regulation of cerebral blood flow[127] , or a direct molecular pathway beyond vacularization, such as influencing N-acetylaspartate, a metabolite exclusively in cell bodies of neurons, given its identified mediating effect between the association of fitness and backward digit span performance [128].

The large, population-based sample of young to middle-aged adults, who have symptom-limited maximal treadmill tests conducted at two examinations 20 years apart and cognitive function tested 25 years later, are the main strengths of the current study. Our study is the first prospective cohort study in middle-aged adults investigating the association between CRF and cognitive function. Our results are generalizable in young to middle-aged adults due to its sampling at baseline which was community-based and balanced by age, race, sex, and educational achievement, and the inclusion of smokers and obese persons. In addition, multiple treadmill testing allows us to study the association between change of Max_{dur} over 20 years and cognitive function, and to further demonstrate the long-term effect of Max_{dur} on cognitive function in young and middle adulthood.

On the other hand, several limitations of this current study should be noted. One is that

identical aspects of cognitive function were not assessed at the baseline examination. Consequently, it is hard to test the temporality of the association between Max_{dur} and cognitive function. Indeed, cognitive function may or may not have changed much since early adulthood (CARDIA baseline) or even childhood. Future CARDIA examinations will be needed to look at the time course of cognitive function as participants become older. As we could only adjust for collected potential confounders in the CARDIA datasets, residual confounding caused by unmeasured confounders may still exist even though CARDIA has collected information on a wide range of variables, including physical activity, diet information, and clinical variables. Also, cautions should be taken while interpreting the independent associations between year 0 Max_{dur} and cognitive function tests, and year 20 $Max_{dur\ and}$ cognitive functions tests, given the strong correlation between year 0 and year 20 Max_{dur} (r=0.74).

In conclusion, CRF predicts cognitive function 25 years later, independent of other factors among apparently healthy middle-aged adults. CRF change over 20 years was positively associated with DSST, but not RAVLT or Stroop test. There is wide variation in cognitive function in our apparently healthy middle aged sample, well before obviously impaired cognitive function begins to appear. This variation in cognitive function is strongly related to a measure of fitness obtained 25 years earlier.

D.5. Tables

Table 1. Baseline characteristics (Mean(SD)/Median(Interquartile range)/Percent) of the cohort (N=2744) by quartiles of Maximal Treadmill Duration at baseline*, the CARDIA Study.

Characteristics	All	1st Quartile (N=603)	2nd Quartile (N=774)	3rd Quartile (N=715)	4th Quartile (N=652)	P for trend†
Maximal Exercise Duration (min)	10.0(2.8)	7.5(2.2)	9.2(2.0)	10.7(2.0)	12.6(2.3)	<0.0001
Age (years)	25.1(3.6)	25.4(3.6)	25.2(3.5)	25.1(3.6)	24.8(3.6)	0.0018
Education (years in school)	14.1(2.3)	13.5(2.2)	14.1(2.2)	14.3(2.1)	14.7(2.3)	<0.0001
BMI (kg/m2)	24.5(4.8)	28.2(6.7)	24.7(4.1)	23.1(3.0)	22.4(2.5)	<0.0001
Weight status						
Normal weight (%)	65.5%	38.0%	58.9%	75.5%	87.7%	<0.0001
Overweight (%)	23.7%	30.2%	30.4%	22.2%	11.4%	
Obese (%)	10.8%	31.8%	10.7%	2.2%	0.9%	
Alcohol intake (ml/day)	11.1(17.8)	12.7(21.0)	10.9(19.2)	10.9(15.7)	10.2(14.8)	0.02
Smoking status						
Never smoker (%)	60.7%	52.2%	58.1%	61.0%	70.6%	<0.0001
Former smoker (%)	14.4%	13.1%	15.3%	15.0%	14.0%	

Current smoker (%)	24.9%	34.7%	26.6%	24.1%	15.5%	
Physical activity score (exercise units)	368 (204-576)	294 (156-471)	324 (190-510)	395 (216-600)	480 (287-709)	<0.0001
TV watching (hours/week)	7.2(9.8)	9.7(11.5)	7.4(9.8)	6.4(8.9)	5.7(8.6)	<0.0001
A priori Diet Quality Score	64.1(13.2)	61.0(11.3)	63.4(12.6)	65.1(13.7)	66.8(14.2)	<0.0001
Systolic Blood Pressure (mmHg)	109.8(10.5)	112.5(11.0)	109.3(10.1)	109.1(10.5)	108.8(10.2)	<0.0001
Diastolic Blood Pressure (mmHg)	68.3(9.3)	69.9(10.5)	67.7(8.8)	67.7(9.0)	68.0(9.1)	0.0009
Lung Function						
Force Vital Capacity (FVC) (L)	4.3(1.0)	4.3(1.0)	4.3(1.0)	4.4(1.0)	4.5(1.0)	<0.0001
Forced expiratory volume in 1 second (FEV1) (L)	3.6(0.8)	3.5(0.8)	3.5(0.8)	3.6(0.8)	3.7(0.8)	<0.0001
FEV1/FVC	83.1(6.4)	82.8(6.7)	83.2(6.5)	83.2(6.5)	83.4(5.9)	0.13
Estimated Glomerular Filtration Rate (ml/min)	119.8(21.7)	120.7(21.1)	120.1(21.6)	119.2(22.2)	119.4(21.7)	0.21
Total Cholesterol (mg/dl)	177.2(33.3)	182.9(34.9)	178.4(34.0)	176.3(33.5)	171.5(29.9)	<0.0001
Diabetes (%)	0.36%	0.8%	0.3%	0.3%	0.2%	0.19

*Race-sex specific quartiles were used with 25th, 50th , 75th percentiles of 10.0, 11.6, 12.9 for black men, 6.0, 7.3, 8.4 for black women, 11.1, 12.6, 13.8 for white men, and 8.0, 9.5, 11.0 for white women;
†T-tests and chi-square tests were used to compare the difference across race-sex specific quartiles.

Table 2. Mean(SD) of cognitive function tests at year 25 by quartiles of Maximal Treadmill Duration at baseline*, CARDIA Study.

Variables	All N=2744	1st Quartile (N=603)	2nd Quartile (N=774)	3rd Quartile (N=715)	4th Quartile (N=652)	P for trend†
Year 25 Cognitive Function						
Rey Auditory-Verbal Learning Test (Words correctly recalled)	8.4(3.2)	7.8(3.3)	8.5(3.2)	8.6(3.2)	8.8(3.2)	<0.0001
Digit Symbol Substitution Test (Digits correctly substituted)	70.7(15.6)	66.0(15.5)	70.3(14.8)	72.2(15.5)	74.0(15.7)	<0.0001
Stroop Test(Seconds to correctly name colors plus number of errors)	44.0(12.3)	46.8(14.1)	43.9(11.0)	43.1(11.8)	42.4(12.2)	<0.0001

* Race-sex specific quartiles were used with 25th, 50th , 75th percentiles of 10.0, 11.6, 12.9 for black men, 6.0, 7.3, 8.4 for black women, 11.1, 12.6, 13.8 for white men, and 8.0, 9.5, 11.0 for white women;
†T-tests were used to compare the difference across race-sex specific quartiles

Table 3. The association between cognitive function tests and Max_{dur} at baseline (N=2744) and at year 20 (N=1955) and its change over 20 years (N=1955), CARDIA.

	Rey Auditory-Verbal Learning Test Words correctly recalled			Digit Symbol Substitution Test Digits correctly substituted			Stroop Test Seconds to correctly name colors plus number of errors		
	Slope	SE	P	Slope	SE	P	Slope	SE	P
Baseline cohort (N=2744)									
Year 0 Max_{dur} (min)									
Minimally adjusted*	0.12	0.03	<.0001	0.92	0.13	<.0001	-0.52	0.11	<.0001
Moderately adjusted £	0.11	0.03	0.002	0.78	0.16	<.0001	-0.28	0.13	0.03
Fully adjusted†	0.10	0.03	0.003	0.75	0.16	<.0001	-0.24	0.13	0.07
Cohort attended year 0 and year 20 treadmill tests (N=1955)									
Year 0 Max_{dur} (min) alone									
Minimally adjusted*	0.12	0.03	0.0003	0.87	0.15	<.0001	-0.38	0.12	0.002
Moderately adjusted £	0.11	0.04	0.008	0.73	0.18	<.0001	-0.20	0.14	0.16
Fully adjusted†	0.10	0.04	0.01	0.70	0.18	0.0001	-0.18	0.15	0.21
Year 20 Max_{dur} (min) alone									
Minimally adjusted*	0.10	0.03	0.001	1.13	0.14	<.0001	-0.46	0.12	<.0001
Moderately adjusted £	0.08	0.04	0.03	1.07	0.16	<.0001	-0.31	0.13	0.02
Fully adjusted†	0.07	0.04	0.04	1.02	0.16	<.0001	-0. 28	0.13	0.03
[Year 20 -Year 0 Max_{dur}] (min) adjusted for Year 0									

Max_{dur} (min)									
Minimally adjusted*	0.06	0.04	0.13	0.97	0.17	<.0001	-0. 37	0.14	0.007
Moderately adjusted £	0.05	0.04	0.22	0.96	0.18	<.0001	-0.28	0.14	0.05
Fully adjusted†	0.04	0.04	0.27	0. 92	0.18	<.0001	-0.26	0.14	0.08

* Minimally adjusted models: adjusted for age, race, sex, attained education level at baseline, and clinical center

£ Moderately adjusted models: further adjusted for dietary pattern, physical activity, smoking, BMI, alcohol consumption, and lung function, in addition to variables in the minimally adjusted models

† Fully adjusted models: further adjusted for blood pressure, cholesterol, diabetes status, glomerular filtration rate, in addition to variables in the moderately adjusted models

D.6. Figures

Figure 1. Adjusted means of cognitive function tests at year 25 within race-sex specific quartiles of Max_{dur} at baseline (N=2744), CARDIA. a. RAVLT £;b. DSST;c.Stroop £

Note:

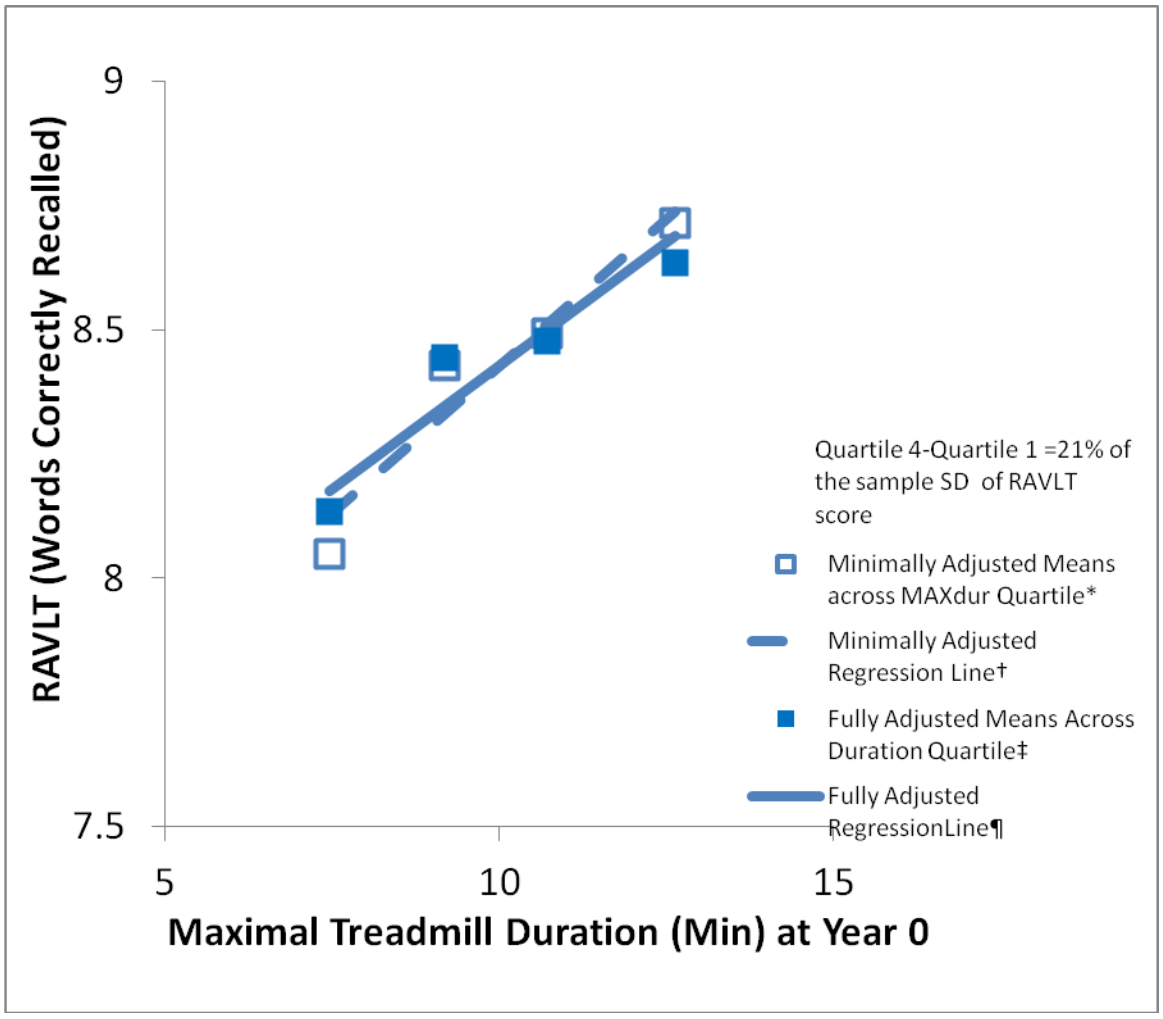
* Minimally adjusted models: adjusted for age, race, sex, attained education level at baseline, and clinical center; As a measure of goodness of fit, means of Max_{dur} within each quartile of Max_{dur} (X axis) were plotted against adjusted means of cognitive function tests, RAVLT, DSST, and Stroop, respectively (Y axis)

† Plotted Max_{dur} (X axis) against cognitive function tests, RAVLT, DSST, and Stroop, respectively (Y axis), both as continuous variables with minimally adjusted models

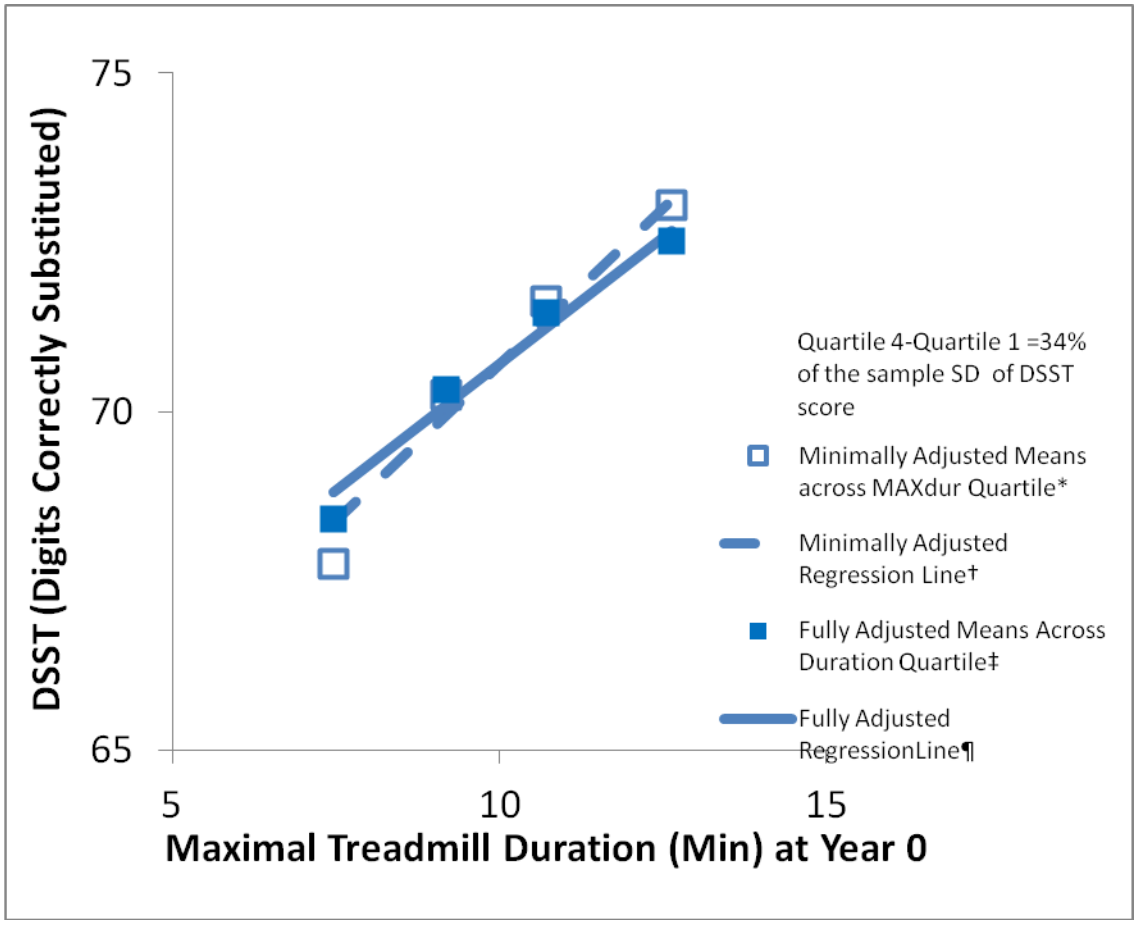
‡ Fully adjusted models: further adjusted for dietary pattern, physical activity, smoking, BMI, alcohol consumption, lung function, blood pressure, cholesterol, diabetes status, glomerular filtration rate, in addition to the variables in the minimally adjusted models. Means were plotted as a measure of goodness of fit.

¶ Plotted Max_{dur} (X axis) against cognitive function tests, RAVLT, DSST, and Stroop, respectively (Y axis), both as continuous variables with fully adjusted models

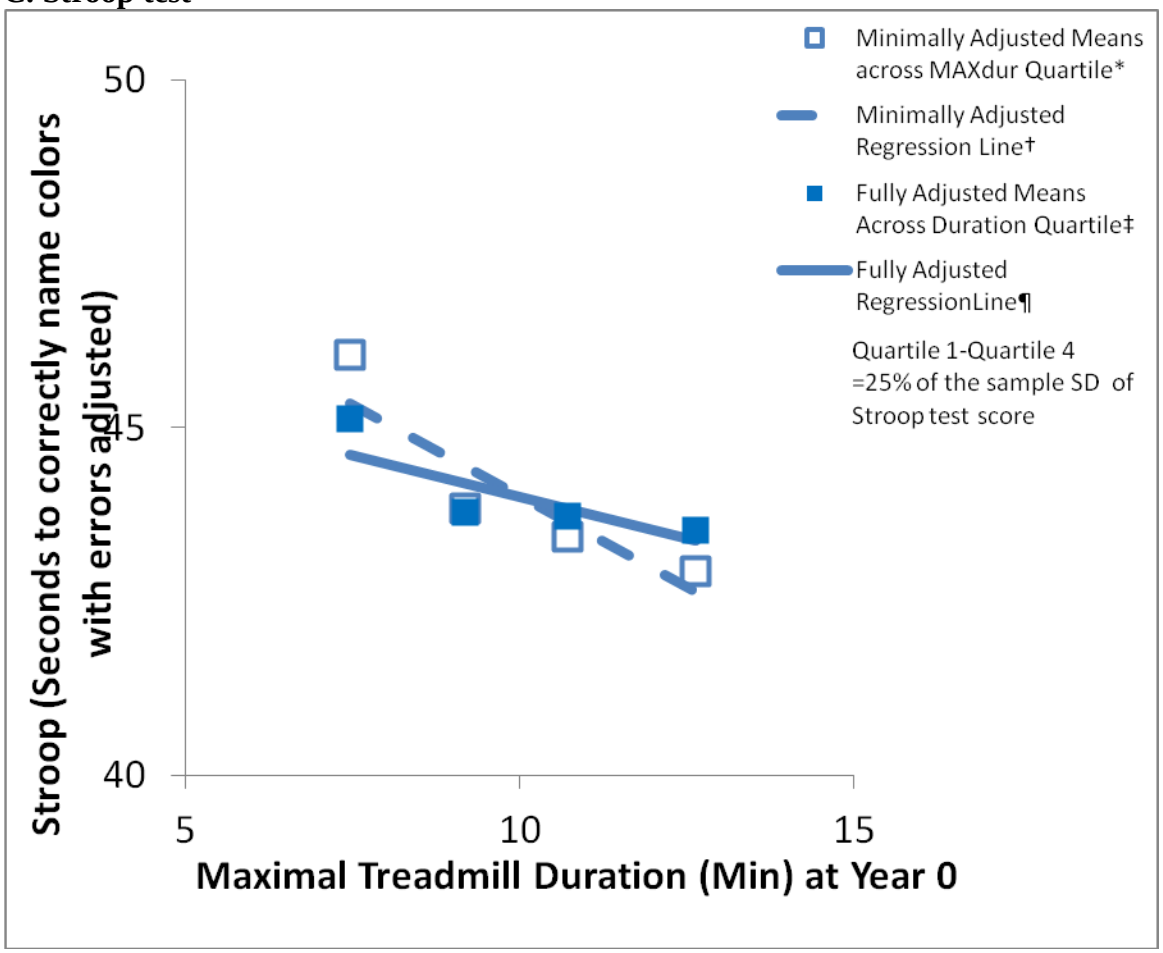
A. RAVLT


9
8.5
8
7.5
RAVLT (Words Correctly Recalled)
5
10
15
Maximal Treadmill Duration (Min) at Year 0
Quartile 4-Quartile 1 =21% of the sample SD of RAVLT score
Minimally Adjusted Means across MAXdur Quartile*
Minimally Adjusted Regression Line†
Fully Adjusted Means Across Duration Quartile‡
Fully Adjusted RegressionLine¶

B. DSST


75
70
65
DSST (Digits Correctly Substituted)
5
10
15
Maximal Treadmill Duration (Min) at Year 0
Quartile 4-Quartile 1 =34% of the sample SD of DSST score
Minimally Adjusted Means across MAXdur Quartile*
Minimally Adjusted Regression Line†
Fully Adjusted Means Across Duration Quartile‡
Fully Adjusted RegressionLine¶

C. Stroop test



E. Manuscript 2 - Cardiorespiratory Fitness in Relation to Brain Atrophy and White Matter Integrity: the CARDIA Study

E.1. Introduction

Cardiorespiratory fitness (CRF), measured by treadmill duration, is related to lower rates of cardiovascular diseases and overall mortality [30,13,29,31,47, 61,28]. Since CRF level may be improved, especially by physical activity and weight loss [17,45], CRF is of interest as a factor that could be intervened upon to promote health.

Brain atrophy as reflected by low brain tissue volume in whole brain or certain regions, and white matter findings on brain MRI, including lower volume, FLAIR/T2 hyperintensity lesions, and reduced integrity as reflected by low fractional anisotropy (FA), have been associated with normal aging, hypertension, cerebral small-vessel disease, and impaired cognitive function, including Alzheimer's disease [68-77,129-141]. Recent studies showed that lower CRF was associated with brain atrophy and white matter changes (especially white matter integrity) in some diseased populations or elderly individuals. In early-stage Alzheimer's disease, higher CRF was associated with reduced brain atrophy, including higher whole brain volume, higher white matter volume, and greater parietal and medial temporal volume[79-81]. Among non-demented elderly, lower CRF was found to be related to regional atrophy in bilateral occipital and temporal cortices [81]. A significant protective effect of CRF on white matter lesion load was found in a study of 715 participants with mean age 65 years [126]. Among patients with multiple sclerosis, it was found that higher CRF level was positively related to white matter integrity (higher focal fractional anisotropy values) [78]. Previous intervention studies

demonstrated that greater aerobic fitness derived during the aerobic exercise training was related to increases in brain white matter volume and white matter integrity in the frontal and temporal lobes [142,143].

To date, the evidence for the associations between CRF and whole brain volume, and especially white matter measurements, is mostly limited to diseased or elderly individuals. Therefore, we propose to investigate these associations among middle-aged adults including blacks as well as whites to gain a better understanding of the pathogenesis of brain atrophy and white matter lesions in adulthood. We hypothesized that greater CRF, defined by longer symptom-limited maximal treadmill test duration (Max_{dur}), is associated with lower odds of having unfavorable brain MRI findings including less whole brain volume, and lower normal tissue volume, more abnormal tissue, and lower integrity in white matter in healthy middle-aged adults.

E.2. Methods

E.2.1. Study design

CARDIA is a multi-center longitudinal cohort study of the evolution of cardiovascular risk in adults initially between the ages of 18 and 30 years at study inception in 1985-1986. Recruitment was at random from the general population in Birmingham, AL, Chicago, IL, and Minneapolis, MN, and from members of the Kaiser Permanente Medical Care Plan in Oakland, CA. The full CARDIA sample at baseline was balanced by age (45% aged 18-24 years; 55% aged 25-30 years), race (52% black; 48% white), sex (46% men; 54%, women), and educational achievement (40% completed ≤12 years;

60% >12 years) [107],[105,106]. Seven follow-up examinations were conducted at years 2, 5, 7, 10, 15, 20 and 25, with 91%, 86%, 81%, 79%, 74%, 72% and 72% of the surviving cohort returning, respectively. The institutional review boards for the protection of human subjects for the participating study sites provided approval for the study, and written informed consent was obtained from all participants. Of 710 participants who had brain MRI measured at year 25, 541 participants who also had eligible treadmill tests at year 20 were included in the study. Participants who did not complete the treadmill test tended to have greater white matter ATV, lower FA, and higher systolic and diastolic blood pressures, but did not differ from those who completed the treadmill test in total brain volume, white matter cerebral blood flow, white matter normal tissue volume, and other CVD risk factors, including diabetes and total cholesterol.

E.2.2. Data Collection

Graded exercise testing

The graded symptom-limited maximal exercise test conducted at year 20 exam followed a modified Balke protocol, consisting of nine 2-minute stages of gradually increasing difficulty [108]. Stage 1 was 2% grade at 3 miles per hour, stages 2-6 were 6, 10, 14, 18, and 22% grade at 3.4 miles per hour, stages 7 and 8 were 22 and 25% grade at 4.2 miles per hour, and stage 9 was 25% grade at 5.6 miles per hour. Maximal duration of symptom-limited exercise on a treadmill (Max_{dur}) was the primary exposure. Max_{dur} is a close approximation of cardiovascular fitness and of the true physiological maximum oxygen consumption per unit time (VO_2max) on a treadmill [27]; nevertheless, functioning of other

body systems also plays a prominent role in Max_{dur} because of the volitional symptom-limitation as the stopping criteria. Max_{dur} can be seen as a measure of treadmill performance potential in the face of the maximal physical exertion that the individual can tolerate. Participants (n= 127) were determined to be ineligible for the treadmill test for the following reasons: history of ischemic heart disease, use of cardiovascular medications (except antihypertensive medication), elevated resting blood pressure (systolic blood pressure>160 mmHg or diastolic blood pressure>100 mmHg), or acute illness with a fever (test was rescheduled for a later date whenever possible)[22]. Criteria for terminating the exercise test included general or leg fatigue, shortness of breath, participant refusal to continue, or certain medical reasons**.** The graded symptom-limited maximal exercise test was also conducted at year 0 exam in 643 participants who had brain MRI at year 25.

Brain MRI white matter measurements

The Brain MRI was conducted at 3 participating field centers (Minneapolis, Oakland, and Birmingham) at the year 25 exam. For each subject, structural (T1, T2 and FLAIR), Diffusion Tensor Imaging (DTI), and Arterial Spin Labeling (ASL) imaging sequences were acquired. T1-weighted volumetric MRI scans were processed according to a standardized protocol for alignment, removal of extra-cerebral tissue, and segmentation into gray and white matter. A multi-parametric automated method, which incorporates information from the T1, T2, and FLAIR scans, has been applied for white matter lesion segmentation [144]. Each T1 image has been automatically parcellated into a set of anatomical regions of interest (ROIs) defined on a standard template image, using

deformable registration [145]. Voxel-wise FA maps were derived from DTI images using standard methods. In addition, in a subset of 386 participants (measured at the Minneapolis and Oakland sites only), cerebral blood flow (CBF) was measured using ASL images. White matter consists of 13 regions of interest, including frontal lobes, temporal lobes, parietal lobes, occipital lobes, basal ganglia, the corpus callosum, and fornix.

Measurements of other variables

Sociodemographic variables, including age, race, sex, education level, cigarette smoking, diet, and alcohol use were obtained by self- and interviewer-administered questionnaires at the year 20 exam[111-113]. An *a priori* diet quality score was derived to represent diet pattern [146-148]. Physical activity level was measured by a separate interviewer-based questionnaire regarding the frequency of 13 different activities during the past 12 months; the activity level was estimated by a physical activity score in "Exercise Units" (EU) [114,115]. Frequency and duration of TV watching was also assessed at year 20 [116]. Body weight was measured using a balance beam scale and height using a vertically mounted metal centimeter ruler and a metal carpenter's square. Body mass index (BMI) was derived from the formula: weight(kg) / height(m)^2. Seated blood pressure was measured three times with an Omron oscillometer after 5 minutes of rest with the average of the last two measurements used in analysis. Concurrent use of β-blocker medications and other anti-hypertensive medication were also obtained from self report, with examination of medication bottles when available, at each time period. Hypertension status at year 20 was determined based on a combination of measured systolic blood pressure >140 mmHg,

diastolic blood pressure>90mmHg, or antihypertensive medication use. Lung function was measured at year 20 using a volume-based spirometer (SensorMedics, Inc., Yorba Linda, CA) and following the standard procedures of the combined American Thoracic Society and the European Thoracic Society guidelines [117,125]. Blood glucose in plasma was measured by standard procedures [105]. Diabetes status at year 20 was determined based on fasting glucose level ≥126 mg/dL, self-report of oral hypoglycemic medications or insulin, or a 2-hour postload glucose ≥200 mg/dL [47].

E.2.3. Statistical analysis

Assumptions of normal distributions of white matter measurements, and covariates were checked. There were large race and sex differences in $Max_{dur.}$ Therefore, baseline characteristics were examined across race-sex specific quartiles of Max_{dur}, with statistical testing using t and X^2 tests. Outcomes of interest were whole brain volume, white matter normal tissue volume, abnormal tissue volume, and integrity represented by fractional anisotropy. Whole brain volume and normal and abnormal tissue volume in total white matter and regions of interest in white matter were standardized by dividing each by the intracranial volume (ICV). Dichotomous variables were derived for whole brain volume, and white matter measurements in total white matter and in each region of interest. Low whole brain volume, low white matter normal tissue volume and low white matter integrity were defined as lower than 15th percentile of the sample values. The same approach was used to define low cerebral blood flow in white matter. High abnormal tissue volume was defined as higher than the 85th percentile of the sample values.

Logistic regression was applied to assess the associations of Max_{dur} with low whole brain volume, and low normal tissue volume, high abnormal tissue, and low integrity in white matter measured 5 years later. Age, race-sex groups, field center, body mass index, smoking status (current, former, never), alcohol consumption levels , diet pattern, physical activity, education, systolic and diastolic blood pressure, diabetes, total cholesterol, and lung function, all at year 20, were further adjusted for to account for potential confounding. Intracranial volume was included in model 2 and model 3 for the analysis of fractional anisotropy. As the study is not powered for area specific analysis, only the consistency of direction of the odds ratios of the association between CRF and white matter brain MRI measurements was considered within the 13 individual regions of interest in white matter; we reported confidence intervals for information, but no significance tests were conducted for individual areas. Whole brain volume and white matter normal tissue volume and fractional anisotropy were further analyzed as continuous variables in multiple linear regressions in sensitivity analysis. Similar analysis was conducted to explore the association between CRF and CBF in the subset of 386.

All statistical testing was performed using two-sided tests with the significance level of type I error (α) set at 0.05. Statistical analyses were performed using the SAS 9.2 (SAS Institute Inc., Cary, NC) statistical software packages.

E.3. Results

The cohort consisted of 541 participants with average age 45.4 years at year 20. Among them 88 (16.3%) were black men, 107 (19.8%) were black women, 161 (29.8%) were

white men, and 185 (34.2%) were white women. The cohort was apparently healthy in terms of lifestyle and clinical measures at year 20 except for an average body mass index of 28.1 kg/m^2 (Table 1). Max_{dur} was significantly different across race-sex groups ($P<0.001$). Max_{dur} was 7.7 (2.6) minutes for all participants; highest for white men 9.6(2.3) and lowest for black women 5.3(2.1). Significant differences in baseline characteristics were observed across race-sex specific quartiles of Max_{dur}. Those who were more fit were more likely to be better educated, thinner, nonsmokers, and physically active. They watched less TV, had a higher quality diet, lower blood pressure, and were less likely to have diabetes (Table 1). At year 25, the mean standardized whole brain volume was 81.4% of ICV (SE: 2.4%), mean standardized white matter normal tissue volume was 38.5% of ICV (SE: 2.0%), and mean fractional anisotropy was 0.31 (0.02). The median of white matter abnormal tissue volume was 0.02% of ICV (interquartile range: 0.008%-0.05%).

In multivariable logistic models adjusted initially for age, race-sex groups, and field center (model 1), Max_{dur} was inversely associated with low whole brain volume with the odds ratio (OR) per 1 minute higher Max_{dur} of 0.82 (95% CI, 0.72-0.93) and low white matter FA with the OR of 0.85 (95% CI, 0.74-0.98), but not significantly associated with white matter normal and abnormal tissue volume. After adjusting for body mass index, smoke, alcohol consumption, diet pattern, physical activity, and education (model 2), the association between higher Max_{dur} and low whole brain volume was further enhanced to an OR of 0.73 (95% CI, 0.62-0.87), and the association between higher Max_{dur} and low FA was enhanced to an OR of 0.80 (95% CI, 0.65-0.97) with further adjustement for ICV.

Additional adjustment for clinical measurements including blood pressure, diabetes, total cholesterol, and lung function (model 3) yielded a slightly attenuated association between higher Max_{dur} and low whole brain volume with the OR of 0.78 (95% CI, 0.66-0.93), and an enhanced association between higher Max_{dur} and low FA with the OR of 0.76 (95% CI, 0.62-0.94). The associations between Max_{dur} and whole brain volume and white matter FA remained significant in the same direction with whole brain volume and white matter FA as continuous variables in all 3 models (slope=7% (SE:2.0%) of an SD of whole brain volume and 5% (SE:1.9%) of an SD of white matter FA, per 1 minute higher Max_{dur}, P=0.0003 for whole brain volume and P=0.006 for white matter FA in model 1). No significant interactions were identified between Max_{dur} and race-sex groups on brain MRI measurements (all P>0.05 with df=3).

The direction of association of Max_{dur} with white matter integrity were consistent in all 13 regions of interest in white matter with the overall white matter, although some confidence intervals did include 1, consistent with lower precision of each measure in a smaller area of the brain (table 3). Additionally, no significant association was found between CRF and CBF in the subset of 386 participants (data not shown). Year 0 Max_{dur} was not significantly associated with these brain MRI measurements in the 643 participants in whom it was measured (data not shown).

E.4. Discussion

In the current study, which has a period-cross-sectional design, higher CRF measured by Max_{dur} at average age 45 was associated with more favorable brain MRI measurements 5

years later. Specifically, those with higher Max_{dur} were less likely to have low whole brain volume and low FA as hypothesized. These associations were independent of demographic, lifestyle and clinical characteristics. Higher CRF was not significantly associated with lower normal tissue volume or higher abnormal tissue volume (hyperintensity) in white matter. No association was observed between CRF measured at average age 25 and the brain MRI measurements 25 years later.

Our findings of a positive association between CRF and whole brain volume and white matter integrity are consistent with previous findings in cross sectional studies and clinical trials in healthy older adults and people with Alzheimer diseases and multiple sclerosis [78-81,126,142,143]. In addition, we previously found that CRF was positively related to cognitive function in the CARDIA Study (the first paper in the dissertation). Better cognitive function has been observed to relate to white matter integrity in several other large population studies of middle-aged and elderly individuals [74-77]. Although these associations of CRF with cognitive function and of cognitive function with white matter characteristics do not necessarily mean that brain MRI parameters would be better in those with higher or improved treadmill duration, the evidence presented here is consistent with the hypotheses that brain volume and white matter integrity might respond to improved CRF. The stronger and significant association of CRF and integrity after adjustment for adiposity, lifestyles, and risk factors for cardiovascular disease and brain aging suggests a negative confounding effect and an independent effect of CRF on whole brain volume, especially on white matter integrity. The lack of association between CRF and white matter normal tissue volume and white matter lesions reflected as

abnormal tissue volume in our study may relate to the age and health of our participants. They were in their middle adulthood and were apparently free of any neurologic conditions such as cognitive impairment or dementia; these conditions are found in those who are most likely to present with low white matter normal tissue volume and white matter lesions[74-77,139,140,140,141].

The observed association between CRF and whole brain volume and white matter integrity independent of other risk factors may be explained by some underlying mechanisms. One possible mechanism is that higher CRF, corresponding to higher maximal amount of oxygen an individual can use at any time, may represent better oxygen supply to the brain which is crucial for the brain to maintain its structure and function[149] . Another possible mechanism is that CRF alters brain volume as well as white matter integrity through regulation of cerebral blood flow. Higher CRF has been found to be related to higher cerebral blood flow [127], While higher cortical cerebral blood flow was significantly associated with better white-matter integrity throughout the brain, low CRF may lead to lethal consequences to brain cells as metabolic demand by local neurons and glial tissue is supported by cerebral blood flow, which suggests that the overall blood supply to the brain is an important indicator of brain health especially white-matter health among adults [149-151] . Although no association between CRF and CBF was found in our exploratory analysis, our analysis was limited because CBF was not assessed in one clinical site; the range of CBF in our study may be limited because the sample of 386 participants from 2 clinics tended to be white, better educated, and more physically active than in those in whom CBF was not measured.

Given the age of our study sample, the definition of low whole brain volume and low normal tissue volume, high abnormal tissue, and low integrity in the white matter may not have clinical significance at this point, however, clinical diseases including hypertension, cerebral small-vessel disease, dementia, cognitive impairment, stroke, and multiple sclerosis have been found to be related to low white matter volume, high abnormal tissue, and low integrity [69-73,77-81].We believe that the dichotomized outcomes defined in our study may represent subclinical brain MRI changes in an apparently healthy middle aged population. In addition, corresponding relations of CRF with the continuous white matter variables gave consistent findings. We would like to follow the participants for future brain MRI measurements to further explore the brain MRI measurements and their changes over time in association with CRF as they enter later adulthood.

Our study is the first study in middle-aged adults investigating the association between CRF and whole brain volume as well as white matter measurements in both white and black participants. The population-based sample of healthy middle-aged adults, who had symptom-limited maximal treadmill tests conducted 5 years before the brain MRI are the main strengths of the current study. Our results are generalizable in middle-aged adults due to its sampling at baseline which was community-based and balanced by age, race, sex, and educational achievement, and the inclusion of smokers and obese persons. One limitation of the current study is that brain MRI was only conducted at year 25 and not assessed at the baseline examination. Therefore, it is not possible to test the temporality of the association between Max_{dur} and white matter measurements over 5 years of follow-

up. Additionally, it is impossible to adjust for baseline white matter measurements when studying the potential predictive effect of Max_{dur} on white matter findings 5 years later. Also, as participants with a known contraindication to an MRI examination, including severe claustrophobia, pacemaker, defibrillator, or any foreign metal objects, and those who cannot fit in an MRI tube due to high BMI were excluded from the MRI exam, the study may be restricted to a slightly healthier subgroup of the CARDIA study with lower BMI and fewer cardiovascular events.

In conclusion, we found that greater CRF measured by Max_{dur} on treadmill was positively associated with whole brain volume and white matter integrity 5 years later independent of other factors among apparently healthy middle-aged adults. The findings suggest that CRF may play a role in the brain structure and function, especially whole brain volume and white matter integrity, in this population. It is an interesting possibility that improvement in CRF through exercise may prevent or at least delay future white matter changes in older adulthood.

E.5. Tables

Table 1. Brain MRI measurements and year 20 characteristics (Mean(SD), Median(Interquartile Range), %) by quartiles of treadmill duration*, CARDIA

		Maximal Treadmill Duration				
Characteristics	All	1st Quartile	2nd Quartile	3rd Quartile	4th Quartile	P for trend†
Age (years)	45.4(3.4)	45.8(3.4)	46.0(3.3)	45.3(3.4)	44.7(3.5)	0.002
Education (years in school)	15.8(2.4)	15.2(2.4)	15.6(2.4)	15.9(2.5)	16.5(2.1)	<0.0001
BMI (kg/m^2)	28.1(7.3)	31.8(6.6)	28.9(4.6)	26.6(4.6)	25.2(10.2)	<0.0001
Alcohol intake (ml/day)	12.5(22.3)	13.1(29.0)	10.9(20.8)	14.7(23.9)	11.3(12.8)	0.88
Smoking status						
Never smoker (%)	64.0%	56.3%	63.6%	67.1%	68.4%	0.002

Former smoker (%)	20.9%	19.5%	20.0%	21.2%	22.8%	
Current smoker (%)	15.1%	24.2%	16.4%	11.7%	8.8%	
Physical activity score (exercise units)	301(179, 538)	220(102, 392)	245(154, 417)	292(180, 532)	507(316, 748)	<0.0001
TV watching (hours/week)*	8.2(11.0)	11.4(13.5)	9.7(11.1)	6.9(9.5)	4.9(8.2)	<0.0001
Dietary Pattern Score	63.4(11.6)	58.9(11.0)	63.2(11.7)	63.6(11.4)	67.6(10.9)	<0.0001
Systolic Blood Pressure (mmHg)	114.0(12.5)	116.2(14.1)	114.3(12.3)	113.5(12.9)	112.2(10.5)	0.008
Diastolic Blood Pressure (mmHg)	70.7(10.3)	73.8(11.1)	71.7(10.3)	69.2(10.3)	68.5(8.4)	<0.0001
Forced expiratory volume in one second (L)	3.1(0.8)	2.9(0.7)	3.1(0.7)	3.2(0.7)	3.3(0.8)	<0.0001
Total Cholesterol	185.7(34.3)	181.1(36.4)	193.0(31.6)	188.4(36.6)	179.9(31.1)	0.47

(mg/dl)						
Diabetes (%)	4.8%	10.9%	2.9%	3.7%	2.2%	0.002
Hypertension (%)	12.4%	25.8%	11.4%	7.3%	5.9%	<0.0001

*Race-sex specific quartiles were used with 25^{th}, 50^{th} , 75^{th} percentiles of 6.7, 8.0, 8.9 for black men, 4.0, 5.0, 6.0 for black women, 8.0,10.0, 11.1 for white men, and 6.0, 7.0, 8.9 for white women;

†T test and X^2-test were used to analyze the statistical differences of the baseline characteristics and white matter measurements across race-sex specific quartiles of $Max_{dur.}$

Table 2. Odds ratios (95% confidence intervals) of low whole brain volume, and low normal tissue volume, high abnormal tissue volume, and low fractional anisotropy [a] in white matter associated with 1 minute longer duration on treadmill test, the CARDIA Study.

	Model	OR(95%CI)	P
Total Brain Tissue Volume			
Low Tissue Volume	1 [b]	0.82(0.72,0.93)	**0.002**
	2 [c]	0.73(0.62,0.87)	**0.0002**
	3 [d]	0.78(0.66,0.93)	**0.004**
White Matter			
Low Normal Tissue Volume	1 [b]	0.91(0.81,1.03)	0.13
	2 [c]	0.86(0.74,1.00)	**0.049**
	3 [d]	0.87(0.74,1.02)	0.08
High Abnormal Tissue Volume	1 [b]	1.01(0.89,1.14)	0.89
	2 [c]	0.95(0.81,1.11)	0.51
	3 [d]	0.94(0.80,1.11)	0.45
Low Fractional Anisotropy	1 [b]	0.85(0.74,0.98)	**0.03**
	2 [c]	0.80(0.65,0.97)	**0.02**
	3 [d]	0.76(0.62,0.94)	**0.01**

[a] Low whole brain volume, low white matter normal tissue volume, and low white matter fractional anisotropy means values lower than 15th percentiles of the sample values ; high white matter abnormal tissue volume means values lower than 85th percentile of the sample values;

[b] Model 1: adjusted for age, race-sex groups, clinical center;

[c] Model 2: additionally adjusted for body mass index, smoke, alcohol consumption, diet, physical activity, and education; adjusted for intracranial volume for fractional anisotropy;

[d] Model 3: additionally adjusted for blood pressure, diabetes, total cholesterol, and lung function; adjusted for intracranial volume for fractional anisotropy;

Table 3. Odds ratios (95% confidence intervals) of low white matter integrity [a] associated with 1 minute duration on treadmill test in regions of interest, the CARDIA.

		Left	Right
	Model	OR(95%)	OR(95%)
Frontal Lobe	1[b]	0.80(0.69,0.92)	0.75(0.62,0.91)
	2[c]	0.69(0.57,0.84)	0.74(0.57,0.95)
	3[d]	0.69(0.56,0.84)	0.71(0.54,0.94)
Temporal Lobe	1	0.83(0.72,0.96)	0.85(0.70,1.02)
	2	0.77(0.63,0.93)	0.83(0.66,1.05)
	3	0.74(0.60,0.91)	0.81(0.63,1.04)
Parietal Lobe	1	0.84(0.72,0.98)	0.90(0.79,1.03)
	2	0.79(0.64,0.97)	0.90(0.76,1.06)
	3	0.78(0.63,0.97)	0.89(0.75,1.06)
Occipital lobe	1	0.93(0.81,1.08)	0.91(0.80,1.04)
	2	0.83(0.69,1.00)	0.91(0.77,1.06)
	3	0.82(0.67,1.00)	0.92(0.78,1.08)
Basal Ganglion	1	0.81(0.71,0.93)	0.88(0.77,0.99)
	2	0.71(0.60,0.85)	0.83(0.70,0.98)
	3	0.73(0.61,0.88)	0.83(0.70,0.98)
Corpus Callosum [e]	1	0.88(0.76,1.02)	
	2	0.80(0.67,0.96)	
	3	0.86(0.70,1.04)	
Fornix	1	0.91(0.81,1.03)	0.93(0.81,1.06)

	2	0.89(0.76,1.04)	0.84(0.71,0.99)
	3	0.94(0.79,1.11)	0.90(0.75,1.07)

[a] Low white matter fractional anisotropy means values lower than 15th percentiles of the sample values; [b] Model 1: adjusted for age, race-sex groups, clinical center;

[c] Model 2: additionally adjusted for body mass index, smoke, alcohol consumption, diet, physical activity, education and intracranial volume;

[d] Model 3: additionally adjusted for blood pressure, diabetes, total cholesterol, and lung function;

[e] Corpus Callosum is located in both brain hemispheres.

F. Manuscript 3 - Cardiorespiratory Fitness and Health-Related Quality of Life: the CARDIA Study

F.1. Introduction

Health-related quality of life (HRQOL) is a broad multidimensional concept that mainly represents an individual's perceived physical health, mental state, level of independence, social relationships, and relationship to the environment[83-85]. HRQOL is widely used in public health to evaluate health care delivery, to assess health care disparities, and to predict future medical health care costs. In clinical medicine, HRQOL is an important measurement used to assess the impact of various health conditions, to evaluate the benefits of patient care, and to examine the effect of target therapeutic interventions [84-86]. It is well known that an individual's HRQOL is substantially influenced by different disease states, such as dementia, Parkinson's disease, cancers and injuries[87-93,152-155], and the related complications and comorbidities,

Previous studies illustrate that cardiorespiratory fitness (CRF), a well known important predictor of cardiovascular disease and overall mortality, [13,29-31,47, 61,28] is associated with HRQOL in patients with mild hypertension, diabetes, or coronary heart disease, and in individuals with a recent history of cardiac rehabilitation, bariatric surgery, or organ transplantation [97-101]. Cross-sectional studies demonstrate that higher CRF is associated with higher levels of the mental and physical functioning dimensions of HRQOL in healthy white participants, particularly among men [97,102-104]. Given the established associations between lower HRQOL and greater likelihood of having a variety of chronic diseases and being mentally or physically impaired, we sought to investigate associations between CRF and low HRQOL in middle-aged adults. We hypothesize that: 1) higher

CRF, measured by maximal treadmill duration (MAX_{dur}), is associated with mental and physical HRQOL, specifically, higher CRF is inversely related to the low MCS and PCS scores; and 2) that participants with higher CRF are less likely to respond unfavorably to individual questions contributing to the the HRQOL scores .

F.2. Methods

F.2.1. Study design

CARDIA is a multi-center longitudinal cohort study of cardiovascular risk factors in adults between the ages of 18 and 30 years at study inception in 1985-1986 recruited from the general population in Birmingham, AL, Chicago, IL, and Minneapolis, MN, and from members of the Kaiser Permanente Medical Care Plan in Oakland, CA. The full CARDIA sample was balanced by age (45% aged 18-24 years; 55% aged 25-30 years), race (52% black; 48% white), sex (46% men; 54%, women), and educational achievement (40% completed ≤12 years; 60% >12 years)[107,105,106]. Seven follow-up examinations were conducted at years 2, 5, 7, 10, 15, 20 and 25, with 91%, 86%, 81%, 79%, 74%, 72% and 72% of the surviving cohort returning, respectively. Symptom-limited treadmill tests were conducted at year 20 as part of the ancillary CARDIA Fitness Study. The institutional review boards for the protection of human subjects for the participating study sites provided approval for the study and written informed consent was obtained from all participants. Of 3549 participants who attended year 20 exam, 3449 had HRQOL assessed and 2699 completed symptom-limited treadmill tests. Of these, 2507 participants with complete information from HRQOL assessments, treadmill

tests and relevant covariates available were included in the current cross-sectional analysis of associations between CRF and HRQOL using year 20 exam data. A subset of 2249 participants who also completed HRQOL questionnaire at year 25 were examined to evaluate associations between year 20 measures of CRF and change of HRQOL over 5 years.

F.2.2. Data collection

Graded exercise testing

The graded symptom-limited maximal exercise test followed a modified Balke protocol, consisting of nine 2-minute stages of gradually increasing difficulty [108]. Stage 1 was 2% grade at 3 miles per hour, stages 2-6 were 6, 10, 14, 18, and 22% grade at 3.4 miles per hour, stages 7 and 8 were 22 and 25% grade at 4.2 miles per hour, and stage 9 was 25% grade at 5.6 miles per hour. Maximal duration of symptom-limited exercise on a treadmill (Max_{dur}) was the primary exposure. Max_{dur} is a close approximation of cardiovascular fitness and of the true physiological maximum oxygen consumption per unit time (VO_2max) on a treadmill [27]; and is considered a measure of exercise capacity in the face of the maximal physical exertion that the individual can tolerate. Participants (n=127 at year 20) were determined to be ineligible for the treadmill test for the following reasons: history of ischemic heart disease, use of cardiovascular medications (except high blood pressure medication), elevated resting blood pressure (systolic blood pressure>160 mmHg or diastolic blood pressure>100 mmHg), or acute illness with a fever (test was rescheduled for a later date whenever possible)[22]. Criteria for terminating the exercise test included general or leg fatigue, shortness of breath, participant refusal to

continue, and certain medical reasons**.**

HRQOL measurements

HRQOL was assessed at year 20 and year 25 in CARDIA study with the Medical Outcomes Study 12-Item Short-Form Health Survey (SF-12) (see table 3). The SF-12 assesses HRQOL by asking twelve Likert scale questions (6 physically oriented and 6 mentally oriented) that measure health-related domains, including physical functioning, bodily pain, general health, physical role, social functioning, vitality, mental health, and role emotional. These health-related domains are further summarized into Physical Component Summary (PCS) and Mental Component Summary (MCS) scores. The PCS score assesses physical functioning, bodily pain, general health and role limitations due to physical problems; while the MCS score assesses social functioning, vitality, mental health and role limitations due to emotional problems. Established norm based scoring algorithms were used to score the SF-12. The PCS and MCS scores are scaled to a mean of 50 and a standard deviation of 10 for the general population. Scores higher than 50 or lower than 50 are considered above or below the average in the general U.S. population. Higher PCS or MCS scores correlate with better HRQOL measured in other ways [156].

Measurements of other variables

Sociodemographic variables, including age, race, sex, educational attainment, cigarette smoking, dietary behavior, and alcohol use were obtained by self- and interviewer-administered questionnaires at year 20 exam visit [111-113] Physical activity level was measured by a separate interviewer-based questionnaire regarding the frequency of 13

different activities during the past 12 months; physical activity levels were estimated by "Exercise Units" (EU) [114,115]. Frequency and duration of TV watching was queried [116]. Body weight was measured using a balance beam scale and height using a vertically mounted metal centimeter ruler and a metal carpenter's square. Body mass index (BMI) was derived from the formula: weight(kg)/ height(m)^2. Seated blood pressure was measured three times with Omron device after 5 minutes of rest with the average of the last two measurements used in analysis. Concurrent use of antihypertensive medications was obtained from self reports, with examination of medication bottles when available, at each time period. Hypertension status at year 20 was determined based on a combination of measured systolic blood pressure >140 mmHg, diastolic blood pressure>90mmHg, or antihypertensive medication use. Lung function was measured at year 20 using a volume-based spirometer (SensorMedics, Inc., Yorba Linda, CA) and following the standard procedures of the combined American Thoracic Society and the European Thoracic Society guidelines [117,125]. Serum blood glucose and plasma total cholesterol were measured by standard procedures [105]. Diabetic status at year 20 was determined based on a combination of measured fasting glucose level ≥126 mg/dL, self-report of oral hypoglycemic medications or insulin, or a 2-hour post-load glucose ≥200 mg/dL[47]. Symptoms of depression were assessed at Years 20 and 25, using the CES-D, with a score ≥ 16 defined as depression [157]. At the year 25 examination, a battery of three standardized tests, including the Rey Auditory Verbal Learning Test, the Digit Symbol Substitution Test, and the Stroop Test, was conducted to measure cognitive function)[122-124].

F.2.3. Statistical Analysis

Assumptions of normal distributions of MCS and PCS scores and covariates were checked. As MCS and PCS scores were left skewed (figure 1), they were presented as medians (inter-quartile range). The outcome of interest was low HRQOL with MCS and PCS dichotomous according to the cutpoint of 40 (1SD below the average in the general U.S. population) for the main analysis [156]. Year 20 HRQOL and characteristics were examined in all participants (N=2507) and across quartiles of CRF. As the levels of CRF were significantly different across four race-sex groups (white and black men and women, $P<0.05$), race-sex specific quartiles of MAX_{dur} were used. The Kruskal-Wallis Test, one-way analysis of variance and chi-square tests were used to compare differences between groups. Multiple adjusted logistic regressions were applied to assess cross-sectional associations of year 20 MAX_{dur} and low HRQOL.. Year 20 HRQOL also served as a prospective baseline for study of the association with year 25 HRQOL Linearity was tested for these associations. Multiple covariates at year 20 were included as potential confounders (i.e. age, sex, race, and study center in model 1, addition of physical activity, smoking, body mass index, and education in model 2, and addition of hypertension status, diabetes status, total cholesterol and lung function in model 3). Depression was further adjusted for the analysis of the association between high CRF and low PCS score, while the year 25 cognitive function was further adjusted for the analysis of the association between high CRF and low MCS and PCS scores at year 25. Interactions between Max_{dur} and race, sex, race-sex groups, and education (high school and lower, some college, and college graduate) on HRQOL (year 20) were tested.

Multiple adjusted logistic regression was used to examine associations between CRF and the 12 individual questions from the SF-12; responses for each question were dichotomized to indicate favorable or adverse status. For example, 'not limited' in climbing several flights of stairs was categorized as favorable and compared with 'limited a little' or 'limited a lot', which were categorized as adverse (Table 3). All statistical testing was performed using two-sided tests with the significance level of type I error (α) set at 0.05. Statistical analyses were performed using the SAS 9.2 (SAS Institute Inc., Cary, NC) statistical software package.

F.3. Results

The average age of the cohort was 45 (3.6) years at the year 20 exam with the median MCS score of 53.8 (interquartile range: 47.6-57.1) and median PCS score of 54.2(50.3,56.1) (Table 1). In this cohort, 425 (17.0%) were black men, 652 (26.0%) were black women, 655 (26.1%) were white men, and 775 (30.9%) were white women. The cohort was apparently healthy in terms of lifestyle (including physical activity, TV watching, and percentage of non-smokers), and clinical measures at year 20 except for an average body mass index of 28.7 kg/m^2 (Table 1). Max_{dur} was 7.3(2.7) minutes for all participants; 7.8(2.2) for black men, 5.0(1.8) for black women, 9.3(2.2) for white men, and 7.2(2.3) for white women. Those with higher Max_{dur} were more likely to have higher MCS and PCS, be better educated, thinner, nonsmoker, and were more physically active. They were also more likely to be normotensive and less likely to have diabetes (Table 1). In the subset of 2249 participants who had HRQOL measured at year 25, the average MCS was 50.4(9.4) and the average PCS was 51.2(8.1). Compared to year 20 HRQOL, a

small decrease in the HRQOL was observed (a decrease of 0.5(9.5) for MCS and 1.0(7.4) for PCS) over the 5 years of follow-up. Correlations between year 20 MCS and PCS was 0.02, between year 20 and year 25 MCS was 0.45, between year 20 and year 25 PCS was 0.52. Correlation between year 20 MCS and CES-D was -0.65 while between year 20 PCS score and CES-D was -0.16.

Higher CRF was significantly associated with low MCS and PCS scores measured concurrently (Table 2). In multivariable logistic models adjusting initially for age, race, sex, and study center (model 1), Max_{dur} at year 20 was inversely associated with both low MCS score measured at year 25 with an odds ratio (OR) per 1 minute higher Max_{dur} of 0.88 (95% CI, 0. 83-0.93), and low PCS score measured at year 20 with an OR of 0.65 (95% CI, 0. 59-0.71) (Table 2). The OR for having low MCS score for 4^{th} quartile versus 1^{st} quartile of Max_{dur} was 0.48 (95% CI, 0.33-0.69), and the OR for having low PCS score was 0.13 (95% CI, 0.07-0.24). After adjustment for physical activity, smoking, body mass index, and education in model 2 and additional adjustment for clinical measurements including hypertension, diabetes, total cholesterol, and lung function in model 3, associations were slightly attenuated (all $P<0.05$). No statistically significant interactions were identified between Max_{dur} at year 20 and HRQOL measured at year 20 according to race, sex, race-sex groups, or education (all $P>0.05$). Additional analysis of the dependent variable high HRQOL (cutpoint 60, that is 1 SD above the population mean) did not show significant association with CRF (data not shown).

Further analysis showed that CRF was prospectively significantly associated with low HRQOL. With additional adjustment for year 20 HRQOL, in model 1 Max_{dur} at year 20

was inversely associated with both low MCS score measured at year 25 with an odds ratio (OR) per 1 minute higher Max_{dur} of 0.88 (95% CI, 0. 82-0.93), and low PCS score with an OR of 0.69 (95% CI, 0. 64-0.75) (Table 2). The OR for having low MCS score for 4^{th} quartile versus 1^{st} quartile of Max_{dur} was 0.51 (95% CI, 0.36-0.74), and the OR for having low PCS score was 0.14 (95% CI, 0.08-0.23). Significant and slightly attenuated associations were obtained in model 2 and model 3 (all $P<0.05$). Also, similar magnitude of association between CRF and low MCS score were obtained with additional adjustment for cognitive function alone, while similar magnitude of association between CRF and low PCS score were obtained with additional adjustment for cognition and depression subsequently (data not shown).In addition, higher CRF was significantly related to lower odds of having adverse responses to individual questions corresponding to MCS score and PCS score except for the item related to calm and peaceful feelings which contributes primarily to MCS score (Table 3). The ORs were between 0.79 and 0.91 for each 1 minute higher on Max_{dur} in relation to adverse responses to questions mainly contributing to MCS score, and the ORs were between 0.68 and 0.81 for the questions mainly contributing to PCS score. Further adjustment for physical activity, smoking, body mass index, education, hypertension, diabetes status, total cholesterol and lung function yielded similar magnitudes of association with individual questions. The associations between higher CRF and the adverse response to the question about "less accomplishment due to emotional problems" became non-significant with additional adjustment for cognitive function (data not shown).

F.4. Discussion

In the current study, higher CRF at middle age was inversely associated with low HRQOL both cross-sectionally and prospectively. These observed associations were independent of demographic, lifestyle, education, lung function, cardiovascular risk factors, and cognition.

Our findings are consistent with those of previous studies. Among 709 males (18-49 yr) in the United States Navy, relative higher levels of CRF were associated with higher levels of MCS score and PCS score of HRQOL measured with SF-12 independent of age, systolic blood pressure, body mass index, smoking habit, alcohol habit [103]. In a Finnish study of 196 middle-aged (aged 40-60 years) men working in construction and industrial occupations including construction and industrial work, CRF estimated with a submaximal exercise test on a cycle-ergometer was associated with the physical functioning dimension of HRQOL [104]. In the Aerobics Center Longitudinal Study, among a relatively large sample of generally well-educated whites from middle to upper socioeconomic (5451 men and 1277 women (20-88 yr)), a significant positive graded dose-response relationship was reported between CRF and the mental dimension of the HRQOL measured by General Well-Being Schedule[102]. Our results further extend the existing evidence to blacks with regard to associations between CRF and MCS and PCS prospectively. Additionally, our findings of no association between CRF and high HRQOL implied that participants obtained or maintained high HRQOL through mechanisms other than CRF and people with low HRQOL are more likely to benefit from high CRF.

We found that traditional cardiovascular risk factors, including smoking, adiposity, hypertension, cholesterol, and diabetes status did not attenuate the association of CRF with overall mental and physical HRQOL. However, we recognize that BMI [158],physical activity[159-161], hypertension[93,162,163], diabetes[152-154,164,165], and total cholesterol[166,167] may be in a causal pathway linking treadmill duration with later HRQOL, so adjustment for them might represent explanation of the mechanism of association, In line with our findings, existing studies, including the Aerobics Center Longitudinal Study and the U.S. male Navy study also showed that smoking, adiposity, blood pressure did not explain the association of CRF with HRQOL[102,103]. . Further, lung function (a predictor of both CRF and HRQOL did not account for our findings[168]. Our data therefore suggest that CRF may influence HRQOL through pathophysiologic mechanisms other than cardiovascular or pulmonary pathways.

Previous studies also demonstrated that higher levels of CRF was associated with more favorable levels of cognitive function, including better memory, psychomotor speed and executive function in elderly and diseased populations; higher levels of CRF was associated with a lower risk of cognitive function decline among healthy but sedentary older adults and those with mild cognitive impairment [62-64]. As cognitive function has been related to lower HRQOL in diseased populations, (e.g. those with coronary artery disease, hypertension, chronic obstructive pulmonary disease, kidney diseases, multiple sclerosis, and cancer [169-174]), it is possible the observed association between CRF and overall HRQOL --particularly the mental dimension -- could be partly explained by cognition. However, our findings showed that cognition did not explain the observed

associations between CRF and the MCS and PCS scores. Also, adjustment for depression didn't significantly attenuate the inverse association between high CRF and low HRQOL demonstrated that this association was not explained by depression either. Additionally, lower CRF has been associated with lower white matter volume and more white matter lesions in some diseased populations and elderly individuals[78],[79-81]. [126]. In a recent French study, among patients with multiple sclerosis, it was found that brain MRI measures were related to HRQOL, with T1-lesion load better correlated with physical dimensions and T2-lesion load better correlated with mental components [175]. Besides, in women with mitral valve prolapse syndrome, increase of serum beta-endorphin, an endogenous opioid peptides that function as neurotransmitters, by treadmill exercise endurance training are related to improvement of quality of life[176]. These suggest that brain structures and exercise induced change on neurotransmitter may play an important role on HRQOL beyond one's cardiovascular risk factors and cognitive function. Study of the associations between CRF and individual questions contributing to HRQOL summary scores is intended to specifically elucidate the functional meaning of the hypothesized association between CRF and the HRQOL summary scores. The significant inverse association between high CRF and adverse response to most of the questions demonstrated that CRF affect most dimensions contributing to one's mental and physical HRQOL. Given the physical demand of performing treadmill testing, it is likely that participants with more favorable performance also provide more favorable responses to questions on the physical dimension of HRQOL. This pathway may explain why overall the associations of CRF and individual questions contributing to PCS and the PCS score

are stronger than the associations of CRF and questions contributing to MCS and the MCS score in our study. Though high CRF is not related to the responses to "calm and peaceful feeling" in the current study, high CRF is inversely related to fewer "regular daily activities limitation due to emotional problems", "less accomplishment due to emotional problems", "downhearted and blue feelings", and "social activities interference", and more feelings of "a lot of energy" 5 years later. Our findings are consistent with previous findings that maintenance of CRF during late middle age helped to protect against the onset of depression complaints, given the similarities of these individual questions to the symptoms of depression complaints and high correlation ($r=0.65$) between the MCS score and depression in our study[177]. Additionally, cognitive function may explain the underlying mechanism of the observed association between high CRF and "less accomplishment due to emotional problems".

Strengths of our study consist of its large community-based biracial cohort balanced by age, race, sex, and educational achievement at enrollment, extensive and standardized data collection on potential confounders which allowed simultaneous adjustments. Also, as HRQOL was measured both at year 20 and year 25, the association between CRF and change in HRQOL over 5 years were assessed. Nevertheless, several limitations of this study should be acknowledged. Residual confounding caused by unmeasured confounders such as socioeconomic status may still exist. Nevertheless, since CARDIA has collected information on a wide range of variables, including demographic, lifestyles, and clinical measurements, and our results were robust to adjustment for midlife educational attainment, it is unlikely that the observed associations are completely due to

residual confounding. Also, functioning of other body systems plays role in Max_{dur} because of the volitional symptom-limitation as the stopping criteria, however, Max_{dur} obtained from a symptom-limited treadmill test is widely used as a close approximation of VO_2max obtained from a maximal treadmill test to measure CRF (r=0.92) [27]. SF-12 is a short form of SF-36, which may not measure mental and physical HRQOL as comprehensive as the original SF-36, however, with its high correlation with SF-36 and shortened format, SF-12 is considered as a validated and practical substitute for the SF-36 [178,179].

In conclusion, greater CRF measured by Max_{dur} on treadmill was associated with higher mental and physical HRQOL, measured by MCS score and PCS score respectively, both cross-sectionally and 5 years later among apparently healthy middle-aged adults including blacks as well as whites. The findings suggest that CRF may play a role in HRQOL in this population. Further interventional studies should be conducted to investigate whether improvement in CRF may improve HRQOL in adults. From a public health stand point, these findings make it possible to better identify individuals at risk for lower HRQOL, and further suggest ways to prevent deterioration of HRQOL later in life.

F.5. Tables

Table 1. Year 20 characteristics (Mean(SD)/Median(Interquartile range)/Percent) of the cohort by quartiles of Maximal treadmill duration [a], the CARDIA Study.

		Maximal Treadmill Duration				
Variables	ALL	1st Quartile (N=659)	2nd Quartile (N=612)	3rd Quartile (N=623)	4th Quartile (N=613)	P-value[b]
Health-Related Quality of Life						
Mental Component Score	53.8(47.6,57.1)	53.3(45.0,57.1)	54.2(47.9,57.2)	53.7(48.4, 57.1)	54.7(48.2,57.8)	0.007
Physical Component Score	54.2(50.3,56.1)	51.0(44.2,54.5)	53.9(50.4,55.9)	54.8(51.7,56.2)	55.9(53.4,57.2)	<0.0001
Age (years)	45.0(3.6)	45.3(3.6)	45.2(3.6)	44.9(3.5)	44.5(3.6)	<0.0001
Education (years in school)	15.8(2.6)	15.0(2.6)	15.6(2.6)	16.0(2.5)	16.7(2.3)	<0.0001
BMI (kg/m^2)	28.7(6.7)	33.6(7.5)	29.3(5.1)	26.8(4.4)	25.0(5.9)	<0.0001
Physical activity score	288	193	245	312	463	<0.0001

(exercise units)	(143, 504)	(83, 348)	(124, 441)	(154, 515)	(265, 694)	
TV watching (hours/week)	8.6(11.5)	11.6(14.0)	8.8(10.9)	7.8(10.1)	6.1(9.5)	<0.0001
Smoking status						
Never smoker (%)	62.7%	54.8%	58.8%	64.2%	73.7%	<0.0001
Former smoker (%)	19.6%	19.1%	21.2%	20.4%	17.5%	
Current smoker (%)	17.7%	26.1%	19.9%	15.4%	8.8%	
Forced expiratory volume in 1 second (FEV1) (L)	3.1(0.8)	2.9(0.8)	3.0(0.7)	3.1(0.8)	3.3(0.8)	<0.0001
Hypertension (%)	16.3%	26.0%	17.8%	13.3%	7.7%	<0.0001
Total Cholesterol (mg/dl)	186.1(34.2)	185.2(36.1)	189.6(34.2)	187.5(34.6)	182.3(31.1)	0.09
Diabetes (%)	5.7%	12.3%	5.7%	3.2%	1.0%	<0.0001

[a] Race-sex specific quartiles were used with 25th, 50th , 75th percentiles of 10.0, 11.6, 13.0 for black men, 6.4, 7.5, 8.5 for black women, 11.2, 12.6, 13.8 for white men, and 8.0, 9.6, 11.0 for white women;

[b] Kruskal-Wallis Test, one-way analysis of variance and chi-square tests were used to compare the difference across race-sex specific quartiles.

Table 2. Odds ratios (95% confidence intervals) for low MCS and PCS scores cross-sectionally and 5 years later per 1 minute higher Max_{dur} on treadmill test, the CARDIA Study.

Models	Low MCS Score[a]		Low PCS Score[a]	
	OR(95%CI)	P	OR(95%CI)	P
Y20 HRQOL	(N=332/2507)		(N=179/2507)	
Model 1[b]	0.88(0.83,0.93)	<.00001	0.65(0.59,0.71)	<0.0001
Model 2[c]	0.88(0.81,0.95)	0.0013	0.69(0.62,0.77)	<0.0001
Model 3[d]	0.87(0.81,0.95)	<0.0001	0.71(0.63,0.79)	<0.0001
Y25 HRQOL	(N=324/2249)		(N=246/2249)	
Model 1	0.88(0.82,0.93)	<0.0001	0.69(0.64,0.75)	<0.0001
Model 2	0.89(0.82,0.96)	0.004	0.70(0.64,0.78)	<0.0001
Model 3	0.89(0.82,0.97)	0.006	0.71(0.64,0.79)	<0.0001

[a]Low MCS score or Low PCS score was defined as 1SD below the average MCS score or PCS score in the general U.S. population (<40);

[b] Model 1 adjusted for age, race, sex, and center of clinic visit; For the prospective study with Y25 HRQOL, Y20 HRQOL were included in the model;

[c] Model 2 further adjusted for physical activity, smoking, body mass index and education;

[d] Model 3 further adjusted for hypertension status, diabetes status, total cholesterol and lung function;

Table 3. Odds ratio of adverse responses to individual question contributing to MCS and PCS 5 years later per 1 minute higher of Max_{dur} on treadmill test, the CARDIA Study.

Questions Contributing Primarily to MCS	Favorable Response	Adverse Response	No. of Adverse Response (%)	OR of Adverse response [a]	P
Less accomplishment due to emotional problems	No	Yes	475(21.1%)	0.90(0.86,0.95)	0.0001
Regular daily activities limitation due to emotional problems	No	Yes	216(9.6%)	0.80(0.74,0.86)	<0.0001
Calm and peaceful feelings	All/Most/A good bit/Some of the time	A little/None of the time	195(8.7%)	0.98(0.91,1.05)	0.49
A lot of energy	All/Most/A good bit/Some of the time	A little/None of the time	199(8.8%)	0.79(0.73,0.86)	<0.0001
Downhearted and blue feelings	A little/None of the time	All/Most/A good bit/Some of the time	585(26.0%)	0.91(0.86,0.95)	<0.0001
Social activities	A little/None of the	All/Most/A good bit/Some of the	425(18.9%)	0.84(0.79,0.89)	<0.0001

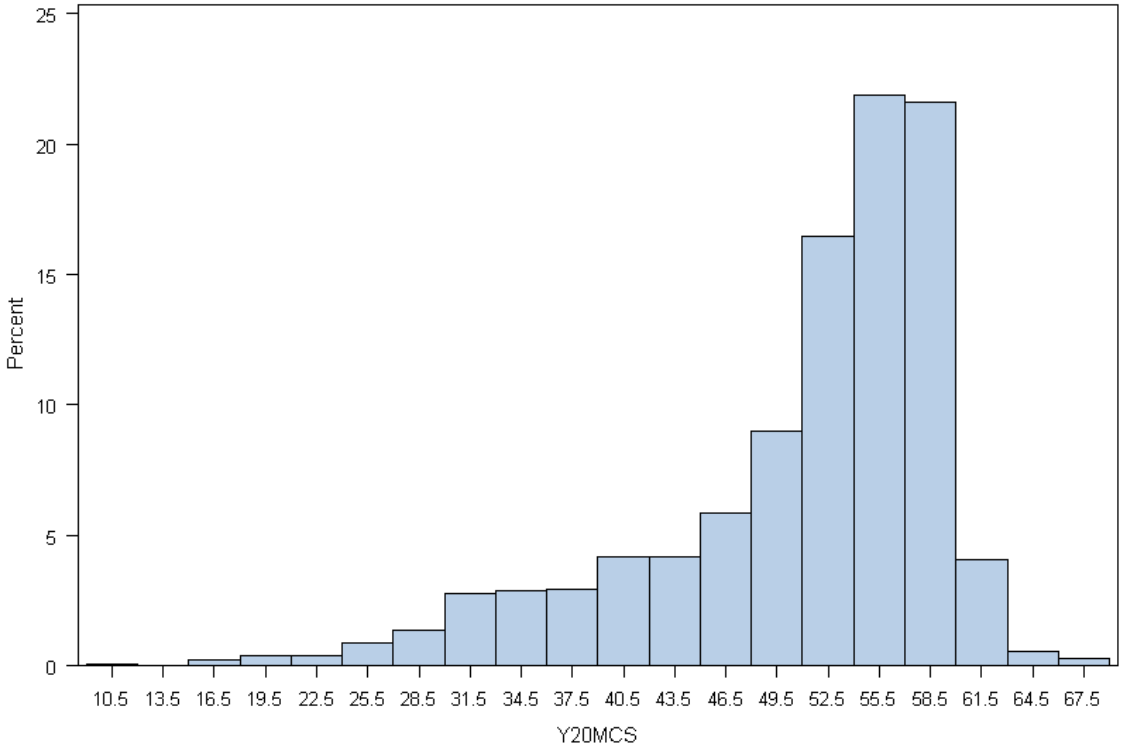
interference	time	time			
Questions Contributing Primarily to PCS					
Health perception	Excellent/Very good/Good	Fair/Poor	237(10.5%)	0.72(0.66,0.78)	<0.0001
Moderate activities	Not limited	Limited a little/Limited a lot	310(13.8%)	0.72(0.67,0.77)	<0.0001
Climbing stairs	Not limited	Limited a little/Limited a lot	512(22.8%)	0.68(0.64,0.73)	<0.0001
Less accomplishment due to physical health	No	Yes	397(17.7%)	0.81(0.76,0.86)	<0.0001
Regular daily activities limitation due to physical health	No	Yes	318(14.1%)	0.80(0.75,0.85)	<0.0001
Normal work interference by pain	Not at all/A little bit	Moderately/Quite a bit/Extremely	325(14.5%)	0.76(0.71,0.81)	<0.0001

a. Model adjusted for age, race, sex, and study center.

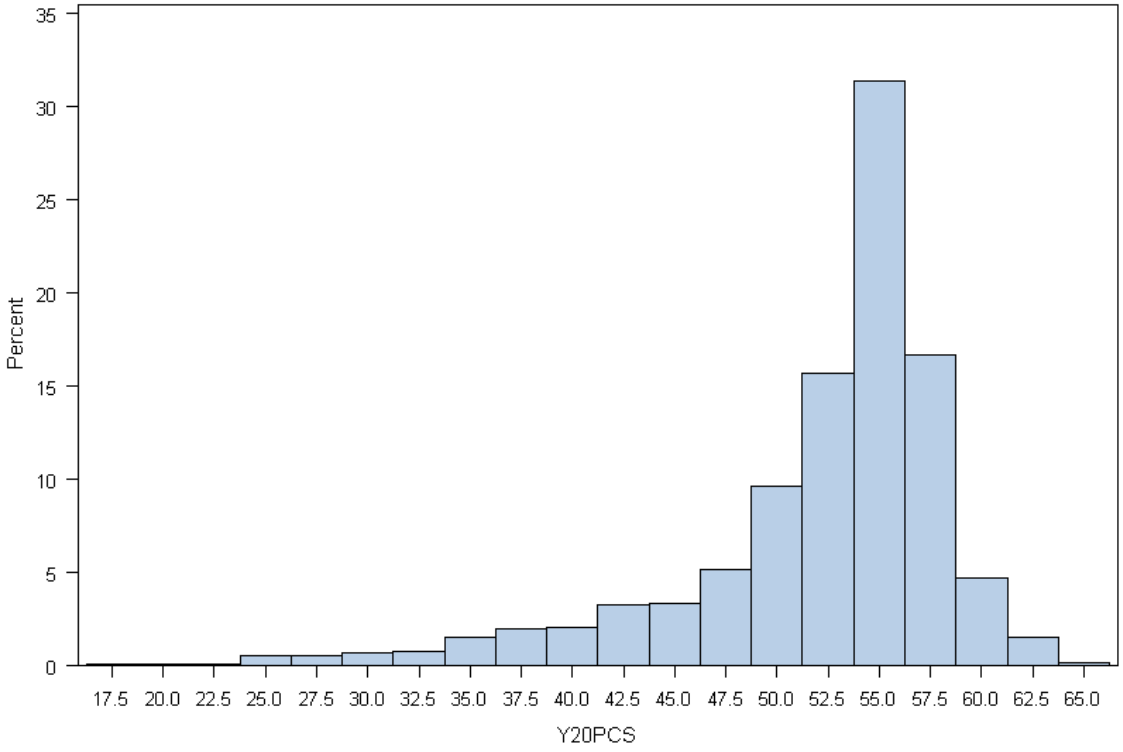
F.6. Figures

Figure 1. Histograms of year 20 MCS and PCS scores.

1a. Year 20 MCS Score



1b. Year 20 PCS Score



G. Overall Conclusions

This dissertation provides insight on the impact of CRF on brain aging and overall health in middle-aged adults. The dissertation supported the hypothesis that CRF was associated with cognitive function, brain MRI findings, and HRQOL, and further expanded previous evidence to middle-aged adults.

We found that higher CRF at average age 25 was positively associated with better performance in RAVLT (verbal memory) and DSST (psychomotor speed) assessed at average age 50, but not Stroop test (executive function). Better DSST performance was also associated with the smaller decrease or improvement of CRF over 20 years. The closer in time the treadmill test is to the cognitive tests (5 years earlier versus 25 years earlier), the stronger the predictive value of the Max_{dur} on the DSST and Stroop test results. Previous studies demonstrated the association of CRF with cognitive function in older adults; our study further confirmed that this association also holds for CRF assessed in young adulthood and cognitive function in middle adulthood. The large, community-based sample of young to middle-aged adults balanced by age, race, sex, and educational achievement at enrollment are the main strength of this study, which provide us more generalizable findings in young to middle adulthood. Additionally, the Max_{dur} measured 20 years apart and the cognitive function tested 25 years later allows us to study whether the change of Max_{dur} over 20 years was associated with cognitive function and to evaluate the long-term effect of Max_{dur} on cognitive function. However, the fact that

cognitive function were not tested at year 0 examination make it hard to test the temporality of the observed associations. It is possible that cognitive function may not have changed much during one's young-to middle aged adulthood, however follow-up cognitive function tests will be needed to assess the temporality of the associations and the time course of cognitive function as people age. Although Max_{dur} may be affected by functioning of other body systems due to volitional symptom as the stopping criteria, with the close correlation between Max_{dur} obtained from a symptom-limited treadmill test and VO2max obtained from a maximal treadmill test (r=0.92), Max_{dur} is widely used as a measure of CRF.

Brain atrophy as reflected by low brain tissue volume in whole brain or certain regions, and white matter findings such as hyperintensity lesions and reduced integrity, have been associated with normal aging, cognitive function impairment, and cerebral small-vessel disease. We found that higher CRF measured at average age 45 was associated with more favorable brain MRI measurements 5 years later. Specifically, higher Max_{dur} was inversely associated with low whole brain volume and reduced white matter integrity but not associated with lower normal tissue volume or hyperintensity lesions in white matter. Our study is the first study in middle-aged adults investigating these associations in both white and black participants. Our findings were consistent with previous studies. Our study participants were middle-aged, and generally free of cerebral vascular diseases at the time of MRI measured, therefore the definition of low whole brain volume and low normal tissue volume, high abnormal tissue, and low integrity in the white matter may not have clinical significance at this moment. However, neurologic diseases including

cerebral small-vessel disease, dementia, cognitive impairment, stroke, and multiple sclerosis, all have been found to be related to low white matter volume, high abnormal tissue, and low integrity, we believe that the dichotomized outcomes defined in our study may represent subclinical brain MRI changes in this apparently healthy middle aged sample. As brain MRI was only conducted at year 25 exam, the temporality of the association between Maxdur and brain MRI measures cannot be assessed. Similar to other studies with brain MRI measurements, our study were limited to a slightly healthier subgroup of the CARDIA study with lower BMI and fewer cardiovascular events, due to the contraindication to an MRI examination.

After exploring the impact of CRF on brain aging, including cognitive function, brain atrophy and white matter measurements, we found that CRF was also related to mental and physical HRQOL. Higher CRF at average age 45 was inversely associated with low HRQOL both cross-sectionally and prospectively. Cognition which was found to be associated with CRF in the same population in earlier study did not explain the observed associations between CRF and the MCS and PCS scores. HRQOL was measured twice at year 20 and year 25 which allowed us to investigate whether CRF at average age 45 predict HRQOL 5 years later. Nevertheless, residual confounding caused by unmeasured confounders such as socioeconomic status may still exist. However, since our results are of strong magnitude and robust to adjustment for demographic, lifestyle, education, lung function, and cardiovascular risk factors, it is unlikely that the observed associations are completely due to residual confounding. SF-12 may not measure mental and physical HRQOL as comprehensive as the original SF-36. However, as SF-12 is highly correlated

with SF-36, SF-12 is applied as a validated substitute for the SF-36 to measure HRQOL in epidemiology studies.

In conclusion, this dissertation demonstrated that CRF was associated with brain aging including cognitive function, brain atrophy, and white matter integrity, and overall mental and physical HRQOL in middle-aged white and black men and women. This study showed the important role of CRF on the overall health besides its known impact on cardiovascular diseases in middle-aged adults. The findings make it possible to better identify individuals at risk for having low cognitive function, unfavorable brain MRI measurement, and low HRQOL at young to middle adulthood. Future interventional studies should be conducted to investigate whether improvement in CRF through exercise will prevent cognitive function decline, brain atrophy, white matter low integrity, and deterioration of HRQOL in middle adulthood.

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