2009

Carotid intima-media thickness and physical and cognitive function in elderly men and women: role of physical activity

John Brent Jr. Rhodes
Louisiana State University and Agricultural and Mechanical College

CAROTID INTIMA-MEDIA THICKNESS AND PHYSICAL AND COGNITIVE FUNCTION IN ELDERLY MEN AND WOMEN: ROLE OF PHYSICAL ACTIVITY

A Thesis
Submitted to the Graduate Faculty of the
Louisiana State University and
Agricultural and Mechanical College
in partial fulfillment of the
requirements for the degree of
Master of Science

in

The Department of Kinesiology

By
John Brent Rhodes, Jr.
B.S., Louisiana State University, 2004
August 2009

DEDICATION

I would like to dedicate this thesis to my wife, Brooke Turnage Rhodes. The support and encouragement that she has given to me throughout my academic endeavors has been paramount to my perseverance and success. I am forever indebted to her.

ACKNOWLEDGEMENTS

I would like to thank Dr. Michael Welsch for his unwavering guidance and support. Without his patience and expertise this thesis would not have been possible. I would also like to thank all of my family and friends for all of their encouragement throughout these past years. Lastly, to my cat Jane, for all of the wonderful breaks she initiated by sitting on the computer keyboard. I will miss her and remember her forever.

TABLE OF CONTENTS

ABSTRACT

The incidence of cognitive impairment in the aging population remains one of the most common morbidities in the elderly, often associated with a decrease in physical function, institutionalization, and death. Several different mechanisms have been proposed, including age-related changes to the vasculature. The purpose of this study was to examine the relationship between physical activity, carotid intima-media thickness and other vascular measures, and measures of cognitive and physical function in older adults. Measures of daily physical activity, vascular structure and function, and cognitive and physical function were examined in 109 participants [age=81±11 yrs]. Daily physical activity was assessed using the Yale Activity Index (YAI) and by calculating total daily energy (TDEE) using the doubly labeled water technique. Vascular structure was assessed using carotid-intima media thickness (CIMT), while cognitive function and physical function were assessed using the Mini-Mental State Examination (MMSE) and the CSPFP-10, respectively. The average YAI score was 37.75±22.78, TDEE was 2133.02±585.68 kcal/d, CIMT was 0.91±0.06 mm, MMSE score 28.17±1.29, and total CSPFP-10 score 42±20. A unique finding was the relationship between daily physical activity levels, vascular measures, and measures of cognitive and physical function, suggesting that those with higher levels of daily physical activity exhibit more favorable vascular, cognitive, and physical measures. In addition, more favorable measures of cognitive and physical function may be due in part to preserved vascular health. In conclusion, the findings of this study strongly suggest that maintaining a more physically active lifestyle may result in physiological changes, and yield vascular, cognitive, and physical functional benefits.

CHAPTER 1-INTRODUCTION

The incidence of cognitive impairment in the aging population is a dimension of the aging process that is recognized and accepted. With a prevalence of 25% in individuals above 65 and 65% in those above 85, it remains as one of the most common morbidities in the elderly (1). Unfortunately, it is also associated with a decrease in physical function, institutionalization and death (2, 3). The mechanism behind age-related cognitive impairment remains mostly unknown, but the degree of cognitive impairment between individuals of the same age can be markedly different, and generalizing age-related cognitive decline should be avoided. Because of the differences in age-related cognitive decline among individuals, one or more factors should be considered, with more rapid decline suggesting a pathological link (4). Cerebral infarction and cerebrohypoperfusion have been associated with cognitive impairment (5). In fact, up to 50% of cases may be explained by cerebral infarcts (3). However, because all physiological decline is multi-factorial in nature, other associated factors must be considered. Age-related cognitive decline may be associated with a lack of physical activity and several studies show that increased cognitive and physical decline are directly related to lower levels of physical activity (6, 7). Several different mechanisms have been proposed as to why physical activity maintains cognitive and physical performance including metabolic, neurological, and vascular mechanisms. Of particular interest to this lab is the relationship between measures of physical activity, vascular structure and health, cognitive function, and physical function. Data from the LSU vascular lab shows that physical activity can modify vascular function even in octogenarians (8). Therefore, it is possible that physical activity interventions may play a role, through vascular modifications, in the maintenance of both cognitive and physical function.

Structural and atherosclerotic abnormalities of the carotid arteries have been associated with cerebral, coronary, and peripheral arterial damage, including ischemic lesions (9, 10). In particular, the intima-media layer of the carotid artery (CIMT) has been shown to increase in thickness with age, considered a normal age-related physiological change of the vasculature (4). While existing relevant studies remain inconclusive for various reasons, the possibility exits that there may be an association between the intima-media thickness of the carotid arteries, physical activity, and normal age-related cognitive and physical decline. There is evidence demonstrating that individuals with higher levels of physical fitness demonstrate higher levels of cognitive function with normal aging (7). The specific mechanisms responsible remain unknown, but it is likely that these mechanisms are related to alterations in the vasculature as a result of physical activity. In fact, it has also been shown that elderly adults with a higher level of fitness exhibit a smaller CIMT than that of their more sedentary peers, suggesting exercise induced vascular remodeling (11). It must be stressed however, that CIMT and any noted changes to CIMT as a result of physical activity do not imply causation, and serve only as a barometer of overall vascular health, with prior studies showing that an increase in CIMT is associated with an increase in overall vascular risk factors (9, 12, 13). Further studies have also yielded significant relationships between vascular structure (CIMT) and physical and cognitive function (14, 15).

While there is a clear link between physical activity and overall functionality, few if any studies have concentrated on the relationship between physical activity and its effects on vascular structure and health, and furthermore how these changes to the vasculature may affect cognitive and physical function. The overall rationale for this study is based on Verbrugge and Jette's *Disablement Process*, which describes how a chronic condition can affect specific body systems causing physiological change, which leads to impairment and ultimately disability.

Disability in this context is defined as “a gap between personal capability and environmental demand” (16). However, Verbrugge and Jette’s model also takes into consideration any environmental or personal factors or “interventions” that may increase or decrease the rate of disablement. When applied to this study, the Verbrugge and Jette model is viewed as such.

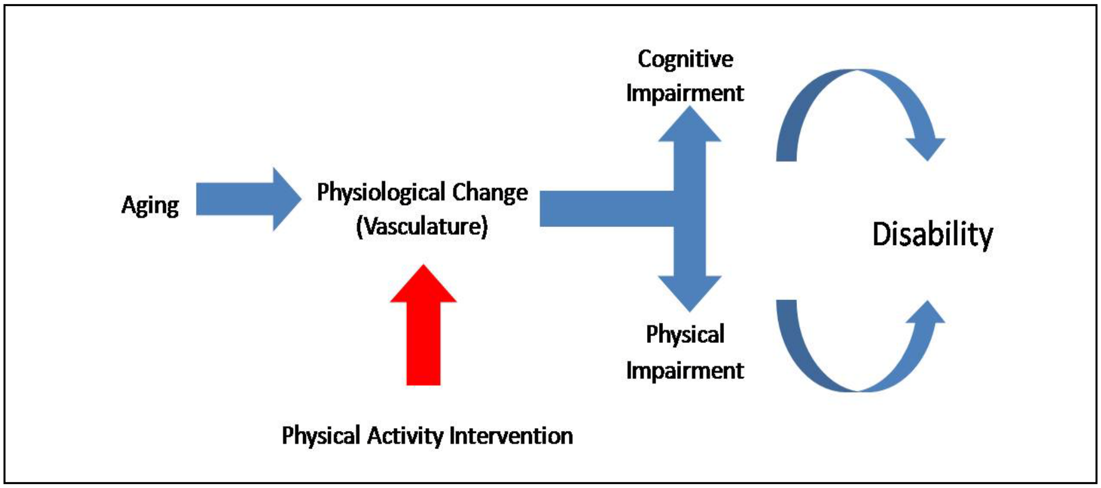

Figure 1. Adapted from Verbrugge and Jette (1994): The Disablement Process

Study Purpose and Hypothesis

Accordingly, the purpose of the study is to examine the relationship between physical activity, carotid intima-media thickness (CIMT), a biomarker of vascular structure and health, cognitive function, and physical function in older adults. It was hypothesized that individuals who are more physically active would have more favorable vascular measures and higher levels of physical and cognitive function.

CHAPTER 2-METHODS

Participants

Participants in this study are from a subset of individuals enrolled in the Louisiana Healthy Aging Study. Sampling of potential participants for the Louisiana Healthy Aging Study is based on a population-based sampling design strategy that included Medicare Beneficiary Enrollment data provided by the Center for Medicare and Medicaid Services. Potential subjects were subsequently recruited from a 40-mile radius from the Pennington Biomedical Research Center in Baton Rouge, La. Exclusion criteria for the present study included individuals in the American Heart Associated Class D (i.e., symptoms or cardiovascular and/or metabolic disease at rest). Each participant signed an informed consent approved by the institutional review boards of the Pennington Biomedical Research Center, The Louisiana State University Health Sciences Center, and the Louisiana State University Agricultural and Mechanical College (8).

Measurements

Physical Activity Assessment

For a subjective assessment of physical activity, the Yale Physical Activity Survey (YPAS) was administered. This interviewer-administered survey is approximately twenty minutes in length, and is designed to evaluate varied activities among varying intensity levels including exercise, recreational, and household settings. There are also a group of questions with categorical responses designed to quickly determine participation in different types of activities (i.e. low intensity walking, vigorous activity, moving, standing, and sitting). Three summary indices are calculated from the YPAS including total time, energy expenditure, and activity dimensions. In addition, there are five subsections. The Total Time Summary Index is expressed as hours per week, and calculates the total time spent on each activity. The Energy Expenditure

Summary Index is calculated by multiplying the time spent on each activity multiplied by an intensity code and summed for all the activities. Finally, the Activity Dimensions Summary Score is calculated by using the five activity subsection dimensions, where the frequency score is multiplied by a duration score for each of the specific five subset activities (low intensity walking, etc.), and then multiplying by a weighting factor. Weighting factors are related to the intensity of the activity subsets. Finally, the final index is calculated as the sum of the five activity subset dimensions (19). For this paper, the final index (Yale Activity Index or YAI) is of particular interest.

For an objective assessment of physical activity, total daily energy expenditure (TDEE) was determined by doubly labeled water (DLW). Upon arrival to the impatient unit of the Pennington Biomedical Research Center, two baseline (*day 1*) urine samples were collected, and participants were then dosed with a mixture of 2.0 g of 10% enriched $H_2\ {}^{18}O$ and 0.12 g of 99% enriched $2H_20$ (Cambridge Isotopes; Cambridge, MA) per kg of estimated total body water (55% of body wt). The dose was followed by a 100-ml tap water rinse. The first two urine samples after dosing (~1.5 and 3 h postdose) were discarded, followed by two urine samples collected at 4.5 h and 6.0 h after dosing. On the mornings of *days 13* and *14*, subjects were instructed to discard their first urine void and collect the second void of the day. Samples were kept refrigerated in airtight containers and were picked up by study staff. Abundance of ^{18}O was measured in duplicate on a Finnigan MAT 252 dual inlet gas isotope ratio mass spectrometer (IRMS), and $^2H_2$ abundance was measured in duplicate on the same IRMS using a Finnigan H/D equilibration device (20). The ^2H and ^{18}O isotope elimination rates were calculated using linear regression following a log transformation, Total body water (N) was determined at the same time zero, obtained from the regression line of the $H_2\ {}^{18}O$ isotope. The rate of CO_2 production was calculated using the equations of Schoeller et al. (20) and later modified as follows: rCO_2 (mol/d) = (N/2.078) (1.007ko-1.041 kd)-0.0246rgf, where rCO_2 is the rate of carbon dioxide production; N is total body water calculated from No/1.007, where N_0 is the ^{18}O dilution space; ko and kd represent he fractional elimination rates of ^{18}O and $^{2}H_2$, respectively; and rgf is the rate of fractionated gaseous evaporative water loss, which is estimated to be 1.05*N (1.007ko-1.041kd). total energy expenditure (TDEE) calculated as follows: TDEE(kcal/d)=22.4 rCO_2 (3.9/RQ=1.10), where RQ represents the respiratory quotient estimated to be 0.86, equal to a healthy, rather low fat diet. Accordingly, the energy equivalent of CO_2, ($EeqCO_2$) was 5.637 kcal/l CO_2 (20).

Vascular Assessment

All brachial artery imaging and analyses were conducted in accordance with the Guidelines set forth by the Brachial Artery Reactivity Task Force (21). Brachial artery ultrasound measures were obtained with participants in the supine position using a 7.5-MHz linear array transducer prior to, during and following 5 minutes of forearm occlusion. Prior to scanning, the participant was instructed to fast for 12 hours. Baseline ultrasound images were obtained after 20 minutes of supine rest. All images were obtained in the longitudinal view, approximately 4 cm proximal to the olecranon process, in the anterior/medial plane. Image depth was initially set at 4 cm, and gain setting were adjusted to provide an optimal view of the anterior and posterior intimal interfaces of the artery and kept constant throughout. The arm of the participant was immobilized and slightly supinated. Forearm occlusion consisted of inflation of a blood pressure cuff, positioned approximately 1 cm distal to the olecranon process, to 200 mmHg for 5 minutes. Images were obtained at rest, and continuously from the final 30 seconds of occlusion until 5 minutes following the release of the blood pressure cuff. In addition, blood pressure and heart rate were monitored throughout the imaging process. All ultrasound images were recorded on compact discs for subsequent analysis.

Resting and peak brachial artery flow velocity measurements were obtained using a pulsed Doppler signal at an angle of approximately 60° to the vessel. Resting velocities were determined following the initial 10 minutes of supine rest. Peak brachial artery flow velocity was assessed immediately following release of the blood pressure cuff.

Data were analyzed using the Brachial Imager software (Medical Imaging Applications, LLC). Arterial diameters were calculated as the man distance between the anterior and posterior wall at the blood vessel interface, with the image in diastole, defined as the peak of the r-wave. Base diameter was defined by the average of 30 seconds of data obtained after 10 minutes of resting conditions. Peak dilation was defined (by visual inspection of the arterial diameter curve) as the largest diameter following release of the occluding cuff. Its value was calculated by the average of 10 images (five seconds) surrounding this highest observable peak.

In order to assess carotid vascular structure, we followed a protocol similar to del Sol et al. of the Rotterdam Study (22). To measure carotid intima media thickness (CIMT), ultrasonography of the common carotid artery, carotid bifurcation, and internal carotid artery of the left and right carotid arteries was performed with a 7.5-MHz linear-array transducer. On a longitudinal, two-dimension ultrasound image of the carotid artery, the anterior and posterior walls of the carotid artery are displayed as two bright white lines separated by a hypoechogenic space. The distance between the leading edge of the first bright line of the far wall and the leading edge of the second bright line indicates the intima-media thickness. For the near wall, the distance between the trailing edge of the first bright line and the trailing edge of the second bright line at the near wall provides the best estimate of the near-wall intima-media thickness. In accordance with the Rotterdam Study ultrasound protocol, a careful search was performed for all interfaces of the near and far walls of the distal common carotid artery, the carotid bifurcation and the internal carotid artery. When an optimal longitudinal image is obtained, it w frozen on the R-Wave of the ECG and stored on videotape. The actual measurements of intima-media thickness were performed off-line. From the videotape, the frozen images were digitized on the screen of a personal computer using additional dedicated software. This procedure has been described in detail previously (22).

The first part of the cohort was measured by manual tracing, while the later part was measured using automated edge detection by a computer. For both techniques, the interfaces of the common carotid artery, the carotid bifurcation, and the internal carotid artery were marked across a length of 10mm. For the common carotid artery measurement, the most distal 10 mm of the common carotid artery before widening into the bifurcation was used. The carotid bifurcation is defined as the part of the artery between the common carotid artery and the tip of the flow divider. The internal carotid artery is defined as the part of the artery after the tip of the flow divider between the internal and the external carotid artery. We will then calculate the mean-intima thickness for common carotid artery only and the mean maximum intima-media thickness over the marked length for both near and far wall for all three arterial segments (22).

The average of three frozen images of each arterial segment was used for this, unless it was found to be impossible to collect three images. When an atherosclerotic plaque is present at the measurement site, it was included in the measurement. For our analysis, we used the maximum carotid intima-media thickness values, which were determined by the mean of the maximum intima-media thickness of near and far-wall measurements of both the left and right side arteries for each of the three arterial segments. If data on one of the walls or one of the sides was missing, maximum thickness of the available wall and side was used (22).

Cognitive Assessment

Cognitive functionality was assessed using the Mini-Mental State Examination (MMSE). The MMSE consists of 11 questions and is completed in 5-10 minutes, untimed, making it a practical and time efficient way to evaluate the cognitive aspects of mental function. The maximum score is 30 and the eleven questions are asked to the participant in their listed order and then scored. For any score less than 25, some degree of dementia should be suspected (17).

The MMSE is organized into two sections. The first, with a maximum score of 21, addresses orientation, memory, and attention, and requires a vocal response. The second, with a maximum score of 9, examines the ability of the participant to name, follow written and verbal commands, copy a complex polygon, and write a sentence (17). Most prior studies have used the MMSE as a unidimesional assessment instrument, but evidence has suggested that the MMSE can be used as a multidimensional assessment instrument, testing specific domains of cognition including concentration, language, orientation, memory, and attention (23). For this paper howver, we will use the total score to assess overall cognitive funtionality.

Physical Function Assessment

Physical function was assessed using the Continuous-Scale Physical Functional Performance Test (CS-PFP-10). The CSPFP-10 is based on the performance of 10 normal activities of daily living which are performed at a maximal effort that is appropriate for the individual. Instructions and measurement protocols for participants were standardized. The individual tasks are scored based on data collected on older adults with a wide range of abilities. Quantification of the task by time, weight carried, or distance is determined by the type of task.

Five separate physical domain scores are averaged to yield a total score of between 1 and 100. Those domains include upper-body strength, lower-body strength, upper-body flexibility, balance and coordination, and endurance.

Completing the CSPFP-10, the Six-Minute Walk Test is a simple, non-invasive test of exercise tolerance that has proven very useful in patient populations. The Six-Minute Walk Test is conducted in a regular hallway which is 40 meters in length. Participants were asked to walk up and down the length of the hallway and achieve the greatest total distance possible in the 6-minute period. Any abnormal symptoms including chest pain or marked dyspnea were to be reported immediately. So that the protocol would be standardized, the participants were not given instructions during the test, but were told of the time remaining to completion (8).

Outcome Measures

Using an associational analysis, we investigated the associations between physical activity, vascular structure, cognitive function, and physical function. The data was based on measurements and test scores from previous studies conducted in the departments of psychology and kinesiology of Louisiana State University for the Louisiana Healthy Aging Study.

The variables of physical activity as determined by the YAI, vascular structure as determined by CIMT and other vascular measures, cognitive function as determined by the MMSE, and physical function as determined by the CSPFP-10 were of main interest.

Statistical Analysis

Statistical analyses were performed using SPSS for Windows (version 17.0). Data are presented as means and SD. To examine the associations between age, markers of vascular health, MSSE scores, and CSPFP-10 scores, Pearson correlation coefficients were calculated. To examine if individuals who are more physically active have more favorable CIMT and higher levels of cognitive and physical function, a MANOVA for 3 levels of activity (based on activity tertiles) was performed. Significance was tested at the 90% confidence level ($p \leq 0.10$).

CHAPTER 3-RESULTS

Participant Characteristics

One-hundred and nine individuals, from the LHAS, completed all facts of the study. The characteristics of these individuals are presented in Table I. Of the 109 participants, 50 were male and 59 were female. The mean age for the study population was 81±11 years. Medical histories revealed that cardiovascular disease was the most prevalent condition, followed by arthritis, and cancer. In particular, approximately 30% of participants had evidence of coronary artery disease (myocardial infarction [16%] and coronary artery bypass [14%]). Consequently, a high number of participants were taking vasoactive agents including antihyperlipidemics (38%), ACE inhibitors (17%), and alpha-adrenergic blockers (20%). The average number of years of education for this population was 14±3 (range 6 to 22 years), indicating the majority of participants had a minimum of a high school degree.

TABLE I. Participant Characteristics

Variable	Mean±SD	Range
Age	81±11	37
Height (cm)	164±11	53
Weight (kg)	76±19	140
Systolic Blood Pressure (mmHg)	139±17	85
Diastolic Blood Pressure (mmHg)	76±10	42

Age-Dependent Changes in Daily Physical Activity. Vascular Dimensions, and Cognitive and Physical Function Scores

Daily Physical Activity Scores

With age, there is a decline in daily physical activity. The rate of decline is defined by the regression equation: Yale Activity Index= -0.384 * (age) + 64.79; r^2=0.16, which equals ~3.5units per decade. TDEE= -31.60 * (age) + 4720.61; r^2=0.41, which equals ~300units per decade. The correlations can be seen in Table II. The total scores for both the YAI and TEE as determined by DLW are found in Table III. The average YAI score was 37.75±22.78 (total units). The TDEE yielded an average of 2133.02±585.68 kcal/d. The YAI and DLW tests were significantly related to each other (r=0.47, p=0.001) and both YAI (r= -0.32, p=0.001) and DLW (r= -0.62, p=0.0001) were significantly and inversely related to age.

TABLE II: Correlation Table

		Age	Yale Index	TDEE	Average CIMT	Carotid Arterial Mass	BAFMD	MMSE	CSPFP-10
Age	R p-value	1 •							
Yale Index	R p-value	-0.32 0.001	1 •						
TDEE	R p-value	-0.60 0.0001	0.47 0.001	1 •					
Average CIMT	R p-value	0.50 0.0001	-0.10 0.319	-0.24 0.12	1 •				
Carotid Arterial Mass	R p-value	0.58 0.0001	-0.06 0.56	-0.27 0.07	0.74 0.0001	1 •			
BAFMD (%)	R p-value	-0.23 0.036	-0.13 0.26	0.04 0.82	-0.12 0.31	-0.3 0.006	1 •		
MMSE	R p-value	-0.45 0.0001	0.12 0.22	0.27 0.08	-0.1 0.28	-0.23 0.02	0.1 0.36	1 •	
CSPFP-10	R p-value	-0.70 0.0001	0.53 0.0001	0.65 0.0001	-0.26 0.01	-0.34 0.0001	0.06 0.57	0.3 0.002	1 •

TABLE III: YAI and TDEE as determined by DLW

Variable	Mean±SD	Range
Yale Activity Index (total units)	37.75±22.78	97
Total Energy Expenditure (kcal/d)	2133.02±585.68	2394

Vascular Dimensions

The carotid artery diameter, average CIMT, carotid arterial mass, and brachial artery flow mediated dilation (BAFMD) responses for the participants are found in Table IV. The average carotid artery diameter at rest during diastole was 8.20±.88 mm. The average CIMT was .91±.06 mm, with the range for the entire group from .79 mm to 1.03 mm. Carotid arterial mass (CMASS) ranged from 8.49 (units) to 17.11 with the average at 12.3±1.7. The average percent change (BAFMD) for the entire group was 4.10%, ranging from 0.00% to 12.71%.

All of the vascular measures were significantly related to age, and this can be seen in Table II. In addition, carotid arterial mass was found to have a significant relationship with BAFMD ($r=-0.30$, $p=0.006$).

TABLE III: Carotid Artery Dimensions and BAFMD

Variable	Mean±SD	Range
Carotid Artery Diameter (mm)	8.2±.87	3.84
Average Carotid Artery IMT	0.91±0.06	0.24
Carotid Arterial Mass	12.34±1.73	8.62
BAFMD (%)	4.10±0.73	12.71

Cognitive Assessment Scores

The descriptive statistics for the composite score of the MMSE are found in Table V. The average composite score was 28.17±1.29, with the range for the entire group from 24 to 30. The composite score of the MMSE was significantly related to age, and this can be seen in Table II.

Table V. Descriptive Statistics for the MMSE

Variable	**Mean±SD**	**Range**
Total Score	28.17±1.29	6

Physical Function Scores

The individual and total scores for the CSPFP-10 are presented in Table VI. With respect to the domain scores for the CSPFP-10, the average upper body flexibility (UBF) (59±21U) yielded the highest average score, whereas lower body strength (LBS) (36±21) was the lowest. The distance walked during the 6-minute walk test averaged 350±138m. The average score for the Total CSPFP-10 was 43±20. As shown in Table II, the individual component and Total PFP-10 scores were significantly associated with age.

All of the physical function scores were significantly related to age, and this can be seen in Table II.

Relationships between Age, Daily Physical Activity, Vascular Dimensions, and Cognitive and Physical Function

The associations between age, physical activity, vascular dimensions, and cognitive and physical function are presented in Table II. As stated above, each of the dependent measures for physical activity, vascular dimensions, and cognitive and physical function were significantly related to age, as shown in the correlation table.

Table VI. Physical Function Scores

Variable	Mean±SD	Range
Balance and Coordination	40±22	86.32
Endurance	43±22	89.23
Lower Body Strength	36±21	82.14
Upper Body Flexibility	59±21	100.00
Upper Body Strength	37±21	84.50
Maximum Walk Distance	350±138	531.12
Total CSPFP-10	42±20	78.44

Notably, there was a strong association between YAI ($r=0.53$, $p=0.0001$), TDEE ($r=0.65$, $p=0.0001$) and the CSPFP-10. However, we did not find any significant relationships between measures of daily physical activity and the vascular dimensions. Cognitive function as determined by the MMSE composite score was significantly and negatively related to Carotid Arterial Mass ($r=-0.23$, $p=0.02$) and positively related to the CSPFP-10 ($r=0.3$, $p=0.002$). These results can be seen in Table II. There were no other significant relationships among the variables.

Examination of Vascular Dimensions, Cognitive Function, and Physical Function based on Physical Activity Levels

The results of the MANOVA comparing CIMT, CMASS, and BAFMD, and MMSE, and CSPFP-10 with the daily activity classifications for YAI revealed significant differences for gender and the YAI classification. On the average men had higher scores on CMASS ($p=0.04$), but lower values for BAFMD ($p=0.005$). Importantly, men in the lowest YAI classification had the highest values for CIMT (p=0.08 vs highest tertile), CMASS (p=0.27 vs highest tertile), and lowest values for BAFMD (p=0.09 vs highest tertile), MMSE (p=0.05 vs highest tertile), and CSPFP-10 (p=0.001 vs highest tertile). The results are depicted in Table VII and figures II, III, IV, and V.

Table VII: Results of the MANOVA

Dependent Variable	TDEE	Mean	Std. Error	95% Confidence Interval	
				Lower Bound	Upper Bound
CIMT	1	.95[a]	.02	.92	.98
	2	.93[a]	.01	.90	.96
	3	.88[a]	.02	.84	.92
CMASS	1	13.47[a]	.50	12.46	14.48
	2	13.27[a]	.42	12.42	14.12
	3	11.64[a]	.63	10.37	12.91
BAFMD	1	2.75[a]	.83	1.08	4.43
	2	4.08[a]	.70	2.66	5.49
	3	5.44[a]	1.04	3.34	7.55
CSPFP-10	1	24.71[a]	5.67	13.25	36.17
	2	41.85[a]	4.78	32.19	51.52
	3	57.39[a]	7.12	42.99	71.79
MMSE	1	24.21[a]	.92	22.35	26.07
	2	27.46[a]	.78	25.89	29.03
	3	28.12[a]	1.16	25.78	30.46

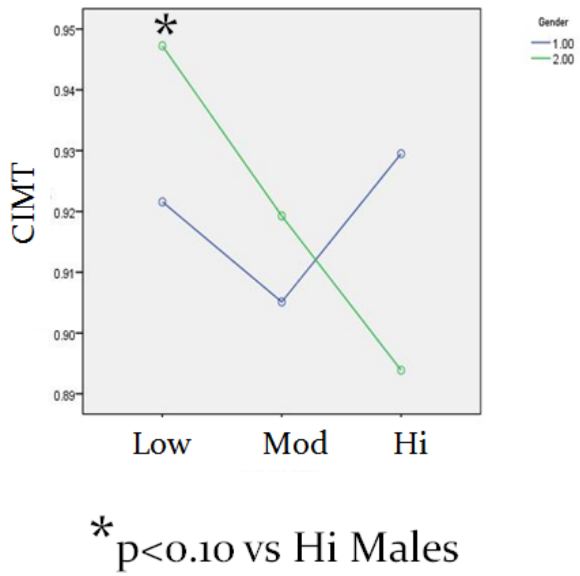

Figure 2: CIMT and Daily Activity (YAI)

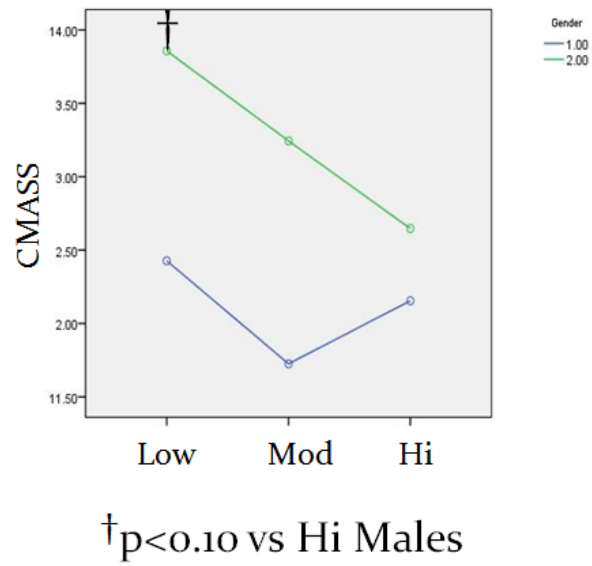

Figure 3: CMASS and Daily Activity (YAI)

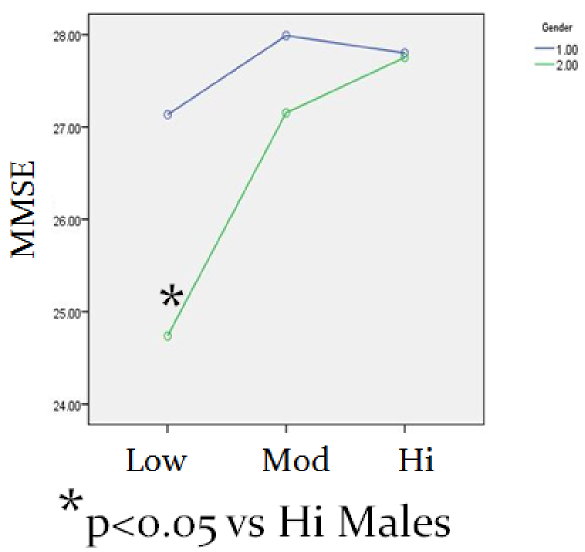

Figure 4: MMSE and Daily Activity (YAI)

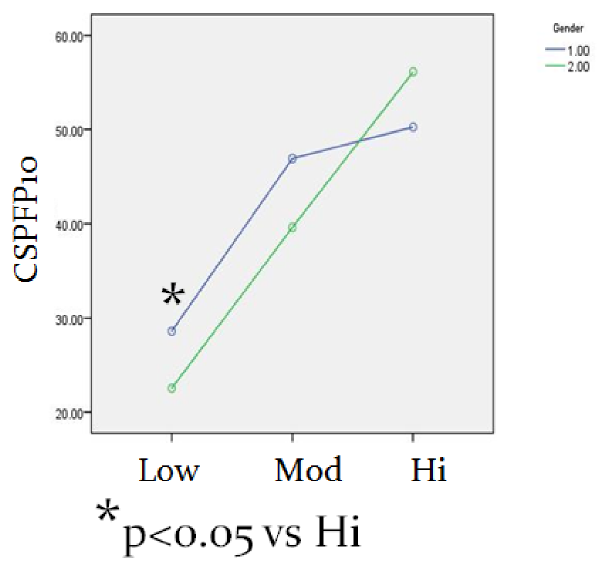

Figure 5: CSPFP-10 and Daily Activity (YAI)

Table VIII: Results of the MANOVA: Gender differences

Dependent Variable	YAI	Gender	Mean	Std. Error	95% Confidence Interval Lower Bound	95% Confidence Interval Upper Bound
CIMT	1	1	.92[a]	.02	.90	.95
		2	.95[a]	.02	.91	.99
	2	1	.91[a]	.02	.87	.94
		2	.92[a]	.02	.89	.95
	3	1	.93[a]	.02	.90	.96
		2	.89[a]	.02	.86	.93
CMASS	1	1	12.43[a]	.45	11.54	13.31
		2	13.86[a]	.60	12.66	15.05
	2	1	11.73[a]	.50	10.74	12.71
		2	13.24[a]	.45	12.36	14.13
	3	1	12.16[a]	.49	11.19	13.12
		2	12.65[a]	.46	11.73	13.57
BAFMD	1	1	5.19[a]	.75	3.70	6.67
		2	1.87[a]	1.01	-.14	3.87
	2	1	5.73[a]	.83	4.08	7.38
		2	2.50[a]	.75	1.02	3.99
	3	1	3.95[a]	.82	2.33	5.57
		2	2.56[a]	.79	1.02	4.12
CSPFP-10	1	1	28.60[a]	4.39	19.89	37.30
		2	22.53[a]	5.92	10.79	34.28
	2	1	46.93[a]	4.87	37.26	56.60
		2	39.62[a]	4.39	30.90	48.33
	3	1	50.26[a]	4.78	40.77	59.75
		2	56.12[a]	4.56	47.07	65.17
MMSE	1	1	27.133[a]	.76	25.62	28.64
		2	24.738[a]	1.03	22.70	26.79
	2	1	27.99[a]	.85	26.31	29.67
		2	27.15[a]	.76	25.64	28.67
	3	1	27.80[a]	.83	26.15	29.45
		2	27.75[a]	.79	26.18	29.32

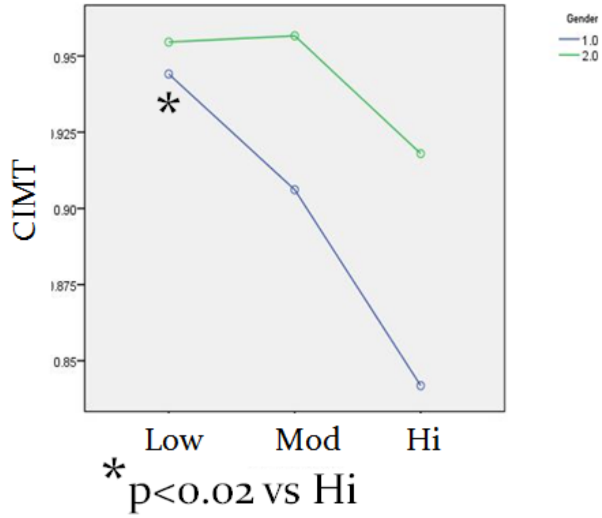

Figure 6: CIMT and Daily Activity (TDEE)

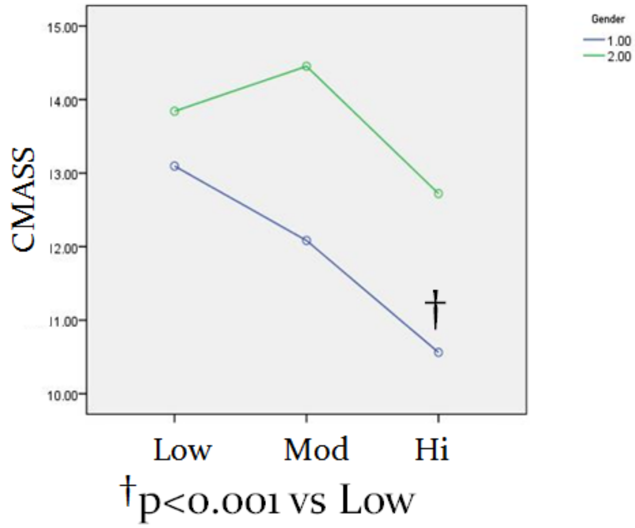

Figure 7: CMASS and Daily Activity

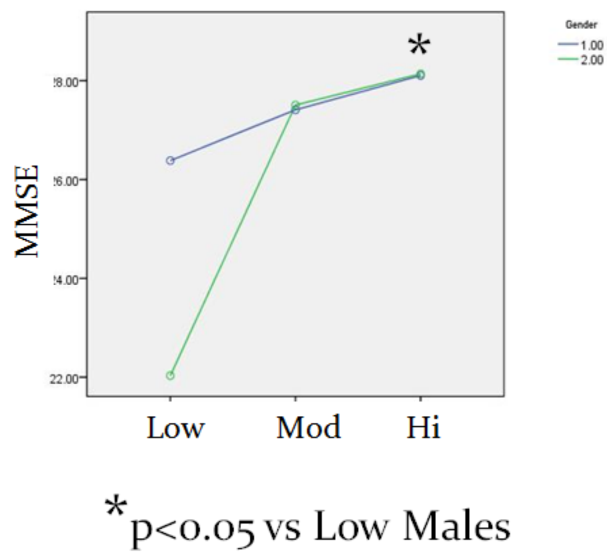

Figure 8: MMSE and Daily Activity (TDEE)

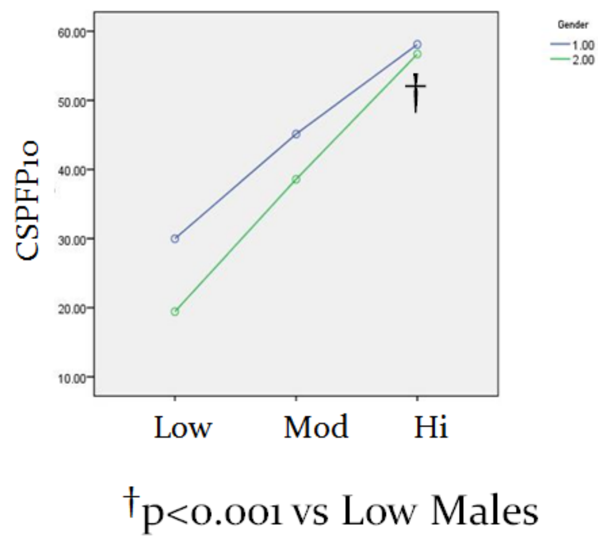

Figure 9: CSPFP-10 and Daily Activity (TDEE)

The results of the MANOVA comparing CIMT, CMASS, and BAFMD, and MMSE, and CSPFP-10 with the daily activity classifications for TDEE revealed significant differences for TDEE classification. On the average those individuals in the higher TDEE tertiles had more values. Interestingly, men in the highest TDEE tertile had significantly lower values for CIMT ($p=0.02$ vs. lowest tertile), CMASS ($p=0.001$ vs. lowest tertile), and higher values for BAFMD ($p=0.03$ vs. lowest tertile), CSPFP10 ($p=0.001$ vs. lowest tertile), and MMSE ($p=0.05$ vs. lowest tertile).

CHAPTER 4: DISCUSSION

The aim of the present study was to examine the relationships between age, vascular structure and function, and physical and cognitive function. The second aim of this study was to examine the effects of daily physical activity status on the above measures. The findings of this study support an age related increase in CIMT and CMASS, and a general decline in other vascular measures as well as a physical and cognitive function. Interestingly, the findings also indicate that those individuals who reportedly participate in greater amounts of daily physical activity exhibit more favorable vascular, and physical and cognitive measures. Of particular interest is that these findings appear to be more evident in men rather than women. The fact that these patterns exist suggests maintenance of higher levels of daily activity throughout the lifespan may aid in preserving physical and cognitive function, perhaps in part secondary to an effect on vascular health.

These findings fit "The Disablement Process" and suggest that lower levels of physical and cognitive function may in part be a consequence of changes in vascular function. However, given the complexity of the aging process we do not rule out the consequences of other physiological changes. The findings of this study are unique in that there have been no other studies to examine daily physical activity, vascular dimensions, and cognitive and physical function.

Influence of Age on Physical Activity Scores

Findings from the Third National Health and Nutrition Examination Survey indicate a low prevalence of physical activity participation among adults over the age of 65 (25). Consistent with this statement, we have also observed a decrease in daily physical activity with increasing age, confirming previous work (20, 27). Daily physical activity decline is associated with deleterious changes in body composition and a decreased ability to perform the essential activities of daily life. Because of these impairments, functional autonomy and independence may be lost, and the risk for mortality significantly higher (20). In addition, it has been shown in separate studies that elderly adults with low levels of daily physical activity have demonstrated less favorable vascular, cognitive, and physical functional measures (6, 7, 28).

For this study, it was decided to measure daily physical activity through both subjective (YAI) and objective (TDEE) measures. Both have been reported to have excellent validity and repeatability (19, 20).

Influence of Age on Vascular Dimensions

Aging is associated with alterations in a number or structural and functional properties of large arteries, including diameter, wall thickness, wall stiffness, and endothelial function (24, 28, 29). Consistent with this statement, we also observed an increase in CIMT with advancing age. These findings further confirm work by others (11, 12, 29). CIMT is useful in cross-sectional studies such as this because it serves as an effective biomarker of overall vascular health. Specifically, changes in CIMT are representative of structural and functional vessel wall properties and generalized atherosclerosis (9, 11, 30).

With advancing aging, it is possible that structural and functional arterial properties interact to produce age-related vascular modifications (11). It has been shown in elderly adults that endothelium-dependent vasodilation is inversely related to CIMT (11). In addition, it has been shown that structural changes to the vasculature including the carotid artery are associated with parallel modifications in endothelium-dependent vasodilation (11). The vascular endothelium is a vital organ that is necessary for vascular tone and homeostasis (31). Dysfunction of the endothelium is characterized primarily by the absence of endothelium derived vasodilatory substances, including nitric oxide, and an increase in endothelium derived contracting factors (31). Thus, the vasodilatory function of the endothelium is impaired. However, the impaired endothelium is also characterized by endothelial “activation”, in which there is a proliferative, proinflammatory, and procoagulative environment present in the artery (31). This vulnerable environment resulting from endothelial dysfunction could be responsible for local vascular modifications and result in additional molecular mechanisms leading to fibrosis, remodeling, and other vascular structural changes (11). Interestingly, this relationship between the structural and functional properties of arteries has been shown through studies involving physical activity interventions, showing that improved endothelial function resulting from physical activity can attenuate the molecular mechanisms that lead to vascular structural changes (11, 32, 33).

Influence of Age on Cognitive Function Scores

Aging is also associated with changes in cognitive function. Consistent with prior studies, we have also observed a negative relationship between age and cognitive function (1, 3, 7). The mechanisms responsible are numerous, and include impaired cerebral circulation, a decrease in dendritic connections, radical oxygen species, and a general inefficiency in the processing functions of the central nervous system (34). The effect of the aging vasculature has been one of particular interest, with “modifiable” risk factors such as the thickening or narrowing of the carotid arteries and blood pressure a target for much research. Interestingly, the age related increase in CIMT has been shown to share a significant relationship with cognitive impairment in previous studies (34). In this study, CIMT values were not significant with MMSE scores, but carotid arterial mass was, and when compared to daily activity levels, those with higher levels of activity exhibited more favorable results on the MMSE. It should be noted that within the daily physical activity tertiles, men showed a more dramatic trend toward more favorable cognitive function as determined by the MMSE than women.

Influence of Age on Physical Function Scores

Overall quality of life and physical functional independence are known to decrease with age. The primary mechanism behind the accelerated age related decrease in physical function is a loss of muscle strength and mass (35). Consistent with this statement, we have observed a negative correlation between age and the PFP-10 as shown in Table II. Interestingly, is has been suggested that while aging itself is thought to be the primary reason for this decline, physical functional decline may be exacerbated by decreases in vigorous physical activity (35). The PFP-10 test measures physical function as it pertains to the execution of a combination of basic and instrumental activities of daily living. Task performance reflects the person's ability as each task is performed at maximal effort within the person's judgment of comfort and safety. Insofar as the CSPFP-10 scoring system is based on a continuous scale with scores between "0" and "100", the regression of CSPFP-10 scores against age in the present study is similar to previous reports (18)**.** This rate of decline in the present sub-sample of the Louisiana Healthy Aging Study Cohort is representative of the entire study sample to date (36). Of further importance is that the examination of the PFP-10 component scores suggests a similar decline across the individual components of the functional tests with age, suggesting that no one particular domain of functional fitness is responsible for lower overall functional performance with advancing age.

Relationship between Physical Activity Scores, Vascular Dimensions, and Cognitive and Physical Function Scores

The major focus of this paper was to examine the relationship between physical activity, CIMT and other vascular measures, cognitive function, and physical function. The data is consistent with the stated hypothesis that individuals with higher levels of physical activity have more favorable CIMT and vascular measures and more favorable measures of cognitive and physical function, the latter possibly a consequence of preserved vascular health. The literature is quite convincing in providing evidence that higher levels of physical activity are associated with reductions in vascular disease, physical disability, and cognitive dysfunction (6, 7, 37). However, the exact volume or type of physical activity needed to harbor these benefits are not completely clear (38). Moreover, the exact mechanism(s) that confers benefits from physical activity in older adults is currently unknown. More than likely the beneficial effects of physical activity do include significant advantageous adaptations in the vasculature, musculature, and neuroendocrine systems (9, 39, 40). In fact, evidence indicates that participation in regular aerobic exercise prevents and even restores age-associated loss in endothelium-dependent vasodilation (41). It is possible that with the maintenance of the endothelium through physical activity, an individual may prevent or even reverse the deleterious development of vascular structural changes (9, 32, 33). Perhaps, the ability to preserve both the structural and functional components of the vasculature contributes to improved local cerebral perfusion and subsequent ability of older adults to maintain cognition later in life (42). It has been shown that increased oxygen availability results in an increase in the metabolism of neurotransmitters, which is associated with an increase in neurophysiological and neuropsychological function (42). Furthermore, it is also possible that maintenance of the vasculature may also contribute to adequate muscle blood flow during physical activity therefore leading to the ability of older adults to perform functional tasks without the early onset of fatigue. Therefore, understanding how to preserve vascular structure and function may provide important clues in regards to "successful" aging, and retention of a high level of cognitive and physical functionality.

As far as we know, this is the first study examine the link between physical activity, vascular dimensions, and cognitive and physical function in an older population. Our findings strongly suggest that maintaining a physically active lifestyle in older age may impart important vascular, cognitive, and physical functional benefits.

Clinical Relevance

According to the most recent predictions by the National Institute on Aging, the United States population aged 65 years or older is expected to double in size within the next 25 years. In fact, by 2030, almost 1 out of every 5 Americans –some 72 million people—was 65 years or older. Moreover, the age group 85 and older is now the fastest growing segment of the U.S. population. Although, the proportion of older Americans with a disability fell significantly from 26.2 percent in 1982 to 19.7 percent in 1999, many are disabled and suffer from chronic conditions. In fact, 14 million people age 65 and older reported some level of disability in Census 2000, mostly linked to a high prevalence of chronic conditions such as heart disease or arthritis (43).

Expanding the current knowledge regarding predictors of "successful" aging is critical in the continued development of preventative and compensatory interventions. It is through the development of such interventions that functional lifespan may be improved and maintained, delaying or preventing disability, and thereby reducing the demands placed on families and communities. This is consistent with the *Disablement Process* as proposed by Verbrugge and Jette, where physical activity as an intervention serves to modify the rate or degree of physiological change (16). Through interventions such as physical activity, the rate or degree of impairment and ultimately disability may be reduced, and physiological reserve and function preserved.

The results of the present study are clinically relevant insofar as they extend our understanding of the influence of physical activity on vascular health and furthermore the influence of vascular health on cognitive and functional fitness. Furthermore, from the results of this study, it is hypothesized that interventions, such as physical training, aimed at preserving or improving overall health may compress morbidity and prolong functional lifespan.

Study Limitations

We remain cautious in our interpretations considering the limitations inherent to a cross sectional design. It is also recognized that the lack of longitudinal data regarding vascular status, physical function, cognitive function, and many other important factors that contribute to the "successful" aging of an individual are not accounted for in the present study. Our intention is to continue our efforts along these lines to account for these shortcomings in future studies. However, we do believe the present observations contribute to the existing literature as it identifies several unique aspects that warrant further discussion and research.

We also recognize our inability to identify possible mechanisms for the changes in vascular measures and the relationship to the functional and cognitive measures in this population. The lack of a mechanistic approach in the current study prevents more sophisticated speculation regarding the development of possible preventative or compensatory interventions for the elderly. However, given our and other researchers findings that exercise training can impart a number of advantageous benefits including but not limited to vascular structure, physical function, and cognitive function (6, 7, 11) we hypothesize that physical training interventions may be an excellent way to maintain and/or improve vascular structure and function and contribute to the preservation of functional ability and independence in the elderly. Our efforts along these lines are continuing in our present studies.

Conclusion

The present study indicates significant relationships between physical activity as determined by the YAI and TDEE, CIMT and other vascular measures, physical function as determined by the CSPFP-10, and cognitive function as determined by the total score of the MMSE. More specifically, when individuals were categorized based on their daily physical activity patterns, those who were most active exhibited the most favorable vascular and cognitive and physical functional measures. These findings strongly suggest that maintaining a physically active lifestyle in older age may result in changes in physiology, and as a result yield further physical and cognitive functional benefits. These benefits due perhaps in part to changes in the vasculature which when combined with other factors may ultimately delay disablement.

REFERENCES

1.Graham, JE, Rockwood K, Beattie BL, Eastwood R, Gauthier S, Tuokko H, et al. Prevalence and severity of cognitive impairment with and without dementia in an elderly population. Lancet. 1997;349:1793-6.

2.Melzer D, Ely M, Brayne C. Cognitive impairment in elderly people: population based estimate of the future in England, Scotland, and Wales. BMJ. 1997; 315: 462.

3.Rockwood K, Wentzel C, Hachinski V, Hogan DB, MacKnight C, McDowell I. Prevalence and outcomes of vascular cognitive impairment. Vascular Cognitive Impairment Investigators of the Canadian Study of Health and Aging. Neurology. 2000; 54: 447-51.

4.Auperin A, Berr C, Bonithon-Kopp C, Touboul PJ, Ruelland I, Ducimetiere P, Alperovitch A. Ultrasonographic assessment of carotid wall characteristics and cognitive functions in a community sample of 59- to 71-year-olds. The EVA Study Group. Stroke. 1996; 8:1290-5.

5.Pullicino PM, Hart J. Cognitive impairment in congestive heart failure? Embolism vs.hypoperfusion. Neurology. 2001; 57:1945-6.

6.Garatachea N, Molinero O, Martinez-Garcia R, Jimenez-Jimenez R, Gonzalez-Gallego J, Marquez S. Feelings of well being in elderly people: Relationship to physical activity and physical function. Arch Gerontal Geriatr.2008; 1845:1-7

7.Angevaren M, Aufdemkampe G, Verhaar HJJ, Aleman A, Vanhees L. Physical Activity and enhanced fitness to improve cognitive function in older people without known cognitive impairment. Cochrane Database of Systematic Reviews. Issue 3 (2008).

8. DeSouza CA, Shapiro LF, Clevenger FA, Dinenno FA, Monagan KD, Tanaka H, Seals DR. Regular aerobic exercise prevents and restores age-related declines in endothelium-dependent vasodilation in healthy men. Circulation. 2000; 102:1351-57.

9.Johnston SC, O'Meara ES, Manolio TA, Lefkowitz D, O'Leary DH, Goldstein S, Carlson MC, Fried LP, Longstreth WT. Cognitive impairment and decline are associated with carotid artery disease in patients without clinically evident cerebrovascular disease. Ann Intern Med.2004;140: 237-47.

10.Waldstein SR, Tankard CF, Maier KJ, Pelletier BA, Snow J, Gardner AW, Macko R, Katzel LI. Peripheral Artery Disease and Cognitive Function. Psychosom Med. 2003; 64: 757-63.

11.Galetta F, Franzoni F, Virdis A, Ghiadoni L, Taddei S, Salvetti A, Santoro G. Endothelium-dependent vasodilation and carotid artery wall remodeling in athletes and sedentary subjects. Atherosclerosis.2006; 186:184-192.

12.Lakatta EG, Levy D. Arterial and Cardiac Aging: Major Shareholders in Cardiovascular Disease Enterprises: Part I: Aging Arteries: A “Set Up” for Vascular Disease. Circulation. 2004; 107:139-146.

13.Bots ML, Hoes AW, Koudstaal PJ, Hofman A, Grobbee DE. Common Carotid Intima-Media Thickness and Risk of Stroke and Myocardial Infarction. Circulation. 1997; 96:1432-1437.

14.Elbaz A, Ripert M, Tavernier B, Février B, Zureik M, Gariépy J, Alpérovitch A, Tzourio C. Common Carotid Artery Intima-Media Thickness, Carotid Plaques, and Walking Speed. Stroke. 2005; 36:2198-2202.

15.Fukuhara M, Matsumura K, Ansai T, Takata Y, Sonoki K, Akifusu S, Wakisaka M, Hamasaki T, Fujisawa K, Yoshida A, Fujii K, Iida M, Takehara T. Prediction of Cognitive Function by Arterial Stiffness in the Very Elderly. Circ J. 2006; 70:756-61.

16.Verbrugge LM, Jette AM. The Disablement process. Sco Sci Med.1994; 38:1-14.

17.Folstein MF, Folstein SE, McHugh PR. “Mini-mental state”. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975; 12:189-98.

18.Welsch MA, Dobrosielski DA, Arce-Esquivel AA, Wood RH, Ravussin E, Rowley C. Jazwinski SM. The Association between Flow-Mediated Dilation and Physical Function in Older Men. Med Sci Sports Exerc. 2008; 40(7):1237-43.

19.Dipietro L, Caspersen CJ, Ostfeld AM, Nadel ER. A survey for assessing physical activity among older adults. Med Sci Sports Exerc. 1993; 25(5):628-42.

20.Johannsen DL, DeLany JP, Frisard MI, Welsch MA, Rowley CK, Fang X, Jazwinski SM, Ravussin E. Physical activity in aging: Comparison among young, aged, and nonagenarian individuals. J Appl Physiol. 2008; 105:495-501

21.Corrretti MC, Anderson TJ, Benjamin EJ, Celermajer D, Charbonneau F, Creager MA, Deanfield J, Drexler H, Gerhard-Herman M, Herrington D, Vallance P, Vita J, Vogel R. Guildelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery: a report of the International Brachial Artery Reactivity Task Force. J Am Coll Cardiol. 2002; 39:257-265.

22.del Sol AI, Bots ML, Grobbee DE, Hofman A, Witteman JCM. Carotid intima-media thickness at different sites: relation to incident myocardial infarction. Eur Heart J. 2002; 23:934-40.

23.Jones RN, Gallo JJ. Dimensions of the Mini-Mental State Examination among community dwelling older adults. Psychol Med. 2000; 30:605-618.

24.Seals DR, DeSouza CA, Donato AJ, Tanaka H. Habitual exercise and arterial aging. J Appl Physiol. 2008; 105:1323-32.

25.Crespo CJ, Keteyian SJ, Heath GW, Sempos CT. Leisure-time physical activity among US adults. Results from the Third National Health and Nutrition Examination Survey. Arch Intern Med. 1996; Jan 8:156:93-8.

26.DiPietro L. Physical Activity in Aging: Changes in Patterns and Their Relationship to Health and Function. J Gerontol. 2001; 56A:13-22.

27.Frisard MI, Fabre JM, Russell RD, King CM, DeLany JP, Wood RH, Ravussin E; for the Louisiana Healthy Aging Study. Physical activity level and physical functionality in nonagenarians compared to individuals aged 60-74 years. J Gerontol A Biol Sci Med Sci. 2007;62:783-8.

28. Welsch MA, Dobrosielski DA, Johannsen DL, Credeur D, Ravussin E, Russell R, Jazwinski SM. Daily Physical Activity and Brachial Artery Flow Mediated Dilation in the Elderly.In Print.

29.Najjar SS, Scuteri A, Lakatta EG. Arterial Aging: is it an immutable risk factor? Hypertension. 2005; 46:454-62.

30.Simons PCG, Algra A, Bots ML, Grobbee DE, van der Graaf Y. Common Carotid Intima-Media Thickness and Arterial Stiffness: Indicators of Cardiovascular Risk in High-Risk Patients: The Smart Study. Circulation. 1999; 100:951-57.

31.Bonetti PO, Lerman LO, Lerman A. Endothelial Dysfunction: A Marker of Atherosclerotic Risk. Arterioscler Throm Vasc Biol. 2003; 23:168-175.

32.Harrison DG. Cellular and molecular mechanisms of endothelial cell dysfunction. J Clin Invest.1997; 100:2153-7

33.Chen SJ, Wu CC, Yen MH. Exercise training activates large-conductance calcium-activated K(+) channels and enhances nitric oxide production in rat mesenteric artery and thoracic aorta. J Biomed Sci. 2001; 8:248-55.

34. Mathiesen EB, Waterloo K, Joakimsen O, Bakke SJ, Jacobsen EA, Bonaa KH. Reduced neuropsychological test performance in asymptomatic carotid stenosis. Neurology.2004; 62:695-710.

35.Fleg JL, Morrell CH, Bos AG, Brant LJ, Talbot LA, Wright JG, Lakatta EG. Accelerated Longitudinal Decline of Aerobic Capacity in Healthy Older Adults. Circulation.2005; 112:674-82.

36.Wood RH, Gardner RE, Ferachi KA, King C, Ermolao A, Cherry KE, Cress ME, Jazwinski SM. Physical function and quality of like in older adults: sex differences. South Med J. 2005; 98:504-12.

37.Paffenbarger RS, Blair SN, Lee IM. A history of physical activity, cardiovascular health and longevity: the scientific contributions of Jeremy N. Morris, DSc, DPH, FRCP. Int J Epidemiol. 2001; 30:1184-92.
38.Kohl HW 3rd. Physical activity and cardiovascular disease: evidence for a dose response. Med Sci Sports Exerc. 2001; 33:S472-83.

39.Walther C, Gielen S, Hambrect R. The effect of exercise training on endothelial function in cardiovascular disease in humans. Exerc Sport Sci Rev. 2004; 32:129-34.

40.Tanaka H, Dinenno FA, Monahan KD, Clevenger CM, DeSouza CA, Seals DR. Aging, habitual exercise, and dynamic arterial compliance. Circulation. 2000; 102:120-75.

41.DeSouza CA, Shapiro Shapiro LF, Clevenger CM, Dinenno FA, Monahan KD, Tanaka H, Seals DR. Regular aerobic exercise prevents and restores age-related declines in endothelium-dependent vasodilation in healthy men. Circulation. 2000; 102:1351-57.

42. Kramer AF, Erickson KI. Capitalizing on cortical plasticity: influence of physical activity on cognition and brain function. Trends Cogn Sci.2007; 11;8:342-46.

43.U.S. Census Bureau. Census Basics 2000. US Government Printing Office, Washington DC, 2002.

VITA

John Brent Rhodes, Jr. received a Bachelor of Science in kinesiology from Louisiana State University in December of 2004. He will receive the Degree of Master of Science in kinesiology in August 2009. He currently resides in New Orleans with his wife Brooke, and will attend the School of Medicine at Louisiana State University Health Sciences Center in New Orleans beginning in August 2009.