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A Multiple-Linear Regression Model to Predict Carotid Artery IMT in a Senior Population of Competitors at the Huntsman World Senior Games

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ABSTRACT

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Carotid intima-media thickness (cIMT) is a valid measure of cardiovascular disease (CVD). Physical activity appears to improve cIMT, however, research is inconclusive. This study investigated the relationship between physical activity (physical activity rating (PA-R)) and cardiovascular fitness (predicted VO_{2max}, perceived functional ability (PFA)) and cIMT. Data collected from 341 seniors ($\geq$50 years) competing in the Huntsman World Senior Games (HWSG) included blood lipids, inflammatory makers, blood glucose, blood pressure (BP) and anthropometric measurements of obesity and central adiposity. Multiple regression analysis was used to determine correlations of measured variables with cIMT. Two of the fitness related variables, PFA ($r \approx 0.1359$; $p = 0.012$) and predicted VO2max ($r \approx 0.1475$; $p = 0.007$) were significantly correlated to cIMT without controlling for confounding factors, but lost significance when adjustments for other CVD risk factors were included. PAR ($r \approx 0.0869$; $p = 0.111$) was not significantly correlated to cIMT. Regression analysis indicated that the most predictive variables of cIMT we investigate were: age ($t = 7.166$, $p = 0.000$), gender ($t = 3.310$, $p = 0.001$), BMI ($t = 1.892$, $p = 0.05$), SBP ($t = 3.952$, $p = 0.000$), total cholesterol (TC) ($t = 4.184$, $p = 0.000$) and triglycerides (TRG) ($t \approx 3.466$, $p = 0.000$), our $R^2 = .299$, thus indicating these 6 variables account for about 30% of the variance in cIMT in seniors competing at HWSG. Physical activity and cardiovascular fitness influence other CVD risk factors and consequently may have an indirect impact on cIMT.

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Introduction

Cardiovascular disease (CVD) is the most prevalent cause of death in the United States (Cobble & Bale, 2010). Atherosclerosis is the most threatening form of heart disease, a major form of CVD, and is responsible for 50% of deaths in the United States (Lusis, 2000). Atherosclerosis is the buildup of lipoproteins, foam cells, smooth muscle cells and necrotic tissue in blood vessel walls, specifically, in the arterial lumen and between the intima and media layers of arteries. Atherosclerotic material is often referred to as plaque. Two common risks are associated with atherosclerotic plaque: hemodynamically significant lesions that restrict blood flow and thromboembolic plaque that can dislodge small clots into the circulation. Plaque can cause cardiovascular events such as myocardial infarction and cerebral vascular accidents.

One way to evaluate the atherosclerotic burden, or the progression of atherosclerosis, is to measure the thickness of the intima and media layers of the arteries (Chambless, et al., 1997; O'Leary, et al., 1999). This can be done non-invasively using B-mode ultrasonography (Anjan K. Sinha, 2002; Cobble & Bale, 2010; Lorenz, Markus, Bots, Rosvall, & Sitzer, 2007; Stein, et al., 2008). The carotid arteries are the location of choice to measure intima-media thickness (IMT) because they are large arteries close to the skin and can be imaged easily. Sonography of the carotid arteries is accurate, reliable, inexpensive and harmless to the subject after repeated measurements (Cobble & Bale, 2010; Stein, et al., 2008). The benefit of sonographic measurements of the carotid artery IMT (cIMT) is that it allows early detection of atherosclerosis, possibly long before adverse symptoms are manifest (Cobble & Bale, 2010). Carotid artery IMT is an important measurement that can successfully predict future cardiovascular events (Chambless, et al., 1997; Lorenz, et al., 2007; O'Leary, et al., 1999; Schmidt, Fagerberg, & Hulthe, 2005; Wyman, Mays, McBride, & Stein, 2006). Carotid artery

IMT is used both clinically and in research to measure atherosclerotic changes over time due to changes in lifestyle and therapeutic interventions (Cobble & Bale, 2010).

Since cIMT is a measure of the progression of atherosclerosis, a decrease in the cIMT suggests a decrease in a person's risk of CVD (Cobble & Bale, 2010). Research generally supports a decrease in the cIMT with increasing levels of physical activity (Eapen, 2009; Ferreira, Twisk, Stehouwer, Van Mechelen, & Kemper, 2003; Kelley, 2005; Kozakova, et al., 2010; Lakka, et al., 2001; Moreau, et al., 2002; Sato, Makita, Uchida, Ishihara, & Majima, 2008; Stein, et al., 2008; Wildman, Schott, Brockwell, Kuller, & Sutton-Tyrrell, 2004). Endurance exercise slowed the progression of IMT in menopausal women (Moreau, et al., 2002; Stein, et al., 2008; Wildman, et al., 2004). Vigorous activity decreased carotid IMT after three years (Kozakova, et al., 2010). Walking 4-5 km/day retarded the progression of carotid artery IMT in subjects with CHD (Sato, et al., 2008). Higher levels of cardiorespiratory fitness was correlated to a slower progression of atherosclerosis in middle-aged men (Lakka, et al., 2001). Increasing physical activity levels during a longitudinal study improved VO_2max and decreased CVD through decreased arterial stiffness (Ferreira, et al., 2003). Less arterial stiffness may be due to decreased atherosclerotic build up in arteries resulting in a smaller cIMT. Thus, improved VO_2max due to increased physical activity levels may decrease cIMT.

Not all research has shown a decrease in cIMT with increasing levels of physical activity. One study positively correlated both endurance and recreational exercise to a better CVD risk profile (BMI, relative body fat %, waist circumference, cholesterol profile, hs-CRP and Leucocytes) but exercise did not decrease vascular wall size compared to the sedentary group (Popovic, et al., 2010). In a two-part cross-sectional study involving a 3-month aerobic exercise

intervention, exercise failed to decrease cIMT (Tanaka, et al., 2002). However, a 3-month intervention may not have been long enough to result in a measureable decrease in cIMT.

There is sufficient evidence supporting a decrease in cIMT associated with increasing levels of physical activity. Maximal oxygen uptake, or VO_2max $(mL \cdot kg^{-1} \cdot min^{-1})$ is a measure of cardiovascular fitness. When performing a submaximal or maximal exercise test to predict or measure VO_2max is not feasible, VO_2max can be predicted using regression models that include non-exercise independent variables. A self-reported physical activity rating (PA-R) (Heil, 1995; Jackson, et al., 1990) and perceived functional ability (PFA) (George, Stone, & Burkett, 1997) are used as indicators of physical activity level and cardiovascular fitness, respectively. Both PA-R and PFA are significant non-exercise independent variables that can be used to predict VO_2max.

Research indicates that cIMT increases with both age and menopause (Anjan K. Sinha, 2002; Kablak-Ziembicka, et al., 2005; Sutton-Tyrrell, 1998), thus seniors have an increased risk of CVD. Although people who are 50 years of age and older could benefit from increased levels of physical activity, they tend to be less active than their younger counterparts (Hooker, et al., 2005). Many seniors may perceive repetitive, endurance or vigorous activity as the only method for increasing cardiovascular health. This, however, is not an accurate assumption. Many sports and recreational activities such as golf, tennis, racquetball and softball are reasonable forms of physical activity that can be used to attain physical activity related health benefits, improve physical fitness and reduce the risk for CVD.

The annual Huntsman World Senior Games (HWSG) in St. George, Utah is a venue that encourages physical activity and sport participation (and competition) in seniors aged 50 years and older. While there is agreement that increased physical activity improves cardiovascular risk

factors there is less agreement on whether physical activity decreases atherosclerosis as measured by cIMT. The purpose of this study was to further investigate the relationships between cIMT and physical activity (as measured by PA-R), cardiovascular fitness (as measured by predicted VO_2max, and PFA), and other traditional risk factors (blood lipids, inflammation, blood glucose control, blood pressure, and anthropometric measures of obesity and central adiposity) in male and female seniors who participated in the HWSG. A secondary purpose of this study was to determine which of the variables of interest were most predictive of cIMT.

Methods

Participants

Three hundred and forty one men (n=199) and women (n=142) over the age of 50 participating in the 2010 annual Huntsman World Senior Games (HWSG) volunteered to participate in this study. Participants were recruited through announcements included in each participant's registration packet and distributed at selected venues, and posters displayed at the Health Fair held each year during the HWSG.

This study was reviewed and approved by the Brigham Young University Institutional Review Board (IRB). Participants voluntarily participated in this study. All study participants read and signed an approved informed consent form prior to participation.

Procedures

Each participant self-reported age, gender, ethnicity, marital status, family health history and tobacco smoking. Participants also indicated on a questionnaire any medications they took, if they had cardiovascular, metabolic or pulmonary disease and checked next to any signs or symptoms listed in the questionnaire describing their health. Participants used additional

questionnaires to self-report PA-R, PFA, and sports participation (specific to participation in the HWSG). The PA-R questionnaire asked participants to rate their level of physical activity over the previous 6-months on a modified 10-point scale (Bradshaw, 2005; George, et al., 1997). The PFA questionnaire included two questions asking participants to rate their ability to walk, jog, or run a distance of 1 mile and 3 miles at a comfortable pace using a 13-point scale (Bradshaw, 2005; George, et al., 1997). The responses to both PFA questions were summed to generate the PFA score.

Each participant's height was measured to the nearest one-quarter inch using a calibrated wall scale weight was measured to the nearest tenth of a pound, using a digital scale (Healthometer Professional, Model 349KLX/320KL, Sunbeam Products, inc., BOCA RATION, FL 33431, USA). Body mass index (BMI; kg/m^2) was calculated from measures of height and weight after being converted to centimeters and kilograms, respectively.

Waist and hip circumferences were measured to the nearest quarter inch while in the standing position using a spring-loaded Gulick tape measure (Thompson, 2010) to give an estimate of central adiposity as described by the American College of Sports Medicine (ACSM). Waist circumference was measured at the narrowest circumference between the umbilicus and the xyphoid process. If there was not a narrowing of the waist within this area, the waist circumference was measured at the level of the umbilicus. The hip circumference was measured at the widest part of the buttocks with both feet together. Each circumference was measured three times. If two of the measurements were the same that number was recorded. If all three measurements were different, then an average of all three measurements was calculated and recorded. If a measurement differed more than half an inch from the other two measurements

then the circumference was re-measured. A waist-to-hip ratio (WHR) was calculated by dividing the recorded waist circumference by the recorded hip circumference.

Resting blood pressure was measured on the left arm using an automated blood pressure monitor (Omron Model HEM-780, Omron Healthcare, Inc., Bannockburn, Illinois, USA). Three consecutive blood pressure measurements were made in the seated position after at least 5 minutes rest. The average systolic and diastolic blood pressure was recorded. Pulse pressure and mean arterial pressure (MAP) were calculated from the recorded systolic and diastolic blood pressures.

VO_2max (mL·kg^{-1}·min^{-1}) was predicted using the following previously published non-exercise regression equation that included age, gender, BMI, PFA, and PA-R as independent variables. $48.073 + (6.178 \times$ gender; females $= 0$, males $= 1) - (0.246 \times$ age$) - (0.619 \times$ BMI$) + (0.712 \times$ PFA$) + (0.671 \times$ PA-R$)$ (George, et al., 1997)

High-Resolution Carotid Ultrasound

Ultrasound images were taken of the right and left common carotid arteries (CCA) using a B-mode, high resolution ultrasonography (Sonosite Titan Ultrasound system, Sonosite Inc., Bothell, WA,USA) following recommended procedures (Touboul et al., 2007, Stein et al., 2008). A 5-MHz transducer was used to generate images at a depth of 3.3 cm as adjusted on the ultrasound machine. Images were taken from an anterior, direct and posterior view of each CCA resulting in a total of six sonographic images for each subject. Images included a longitudinal view of all or a portion of the common carotid bifurcation and the segment of the CCA proximal to it. Both the near and far walls of the CCA were visualized. Each image was stored and later analyzed to determine the average IMT using proprietary automated edge detection software (SonoCalc Version 4.1.0) using methods consistent with those previously described (Touboul et

al., 2007, Stein et al., 2008). When automated analysis was not possible, manual measurement of the cIMT was done according to Fritz's (Hajri, et al., 2007) protocol. The IMT was measured over a 10 mm segment of the far wall of the CCA proximal to the carotid bifurcation. The IMT for each image was recorded and the average IMT for all six images was recorded as the average cIMT.

Prior to this study, the sonographers capturing and measuring images in our study established reliability of their measurements. To do this, sonographic images of the CCA of 100 subjects were captured by the two sonographers. In addition, each sonographer analyzed images captured by him as well as images captured by the other sonographer. Calculation of an accurate intraclass correlation coeficient (ICC) reduces to a method of computing estimates of the variances associated with the different sources of variability. ICC was calculated as the variance due to subjects divided by the sum of the variances associated with the five sources of variability: subjects, sonographer, trial, sonographer x trial, and random error. Bayesian statistical methods were used to compute the ICC. Markov chain Monter Carlo methods were implemented using the computer program WinBUGS (Lunn et al., 2000) to obtain posterior distributions of variables of interest. Posterior distributions naturally yield interval estimates of complicated combinations of variance components that provide a better representation of the reliability of a measurement. Variance due to trial and sonographer x trial were essentially zero so the ICC was calculated as the variance due to subjects divided by the variance due to subjects, sonographer, and random error. The ICC is based on 1000 iterations and 10,000 final draws from the appropriate posterior distributions. The ICC and 95% credible interval was calculated to be 0.86 and 0.728, 0.920 respectively.

Blood Tests

Participants were instructed to fast 8-12 hours before having their blood drawn. Approximately, 17.5 mL of blood were drawn by trained phlebotomists. Assays included a lipid panel (total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), very low-density lipoprotein cholesterol (VLDL-C), triglycerides), fasting blood glucose (FBG), high sensitivity C-reactive protein (hs-CRP) and hemoglobin A1C (HbA1C). The TCHDL ratio was calculated by dividing TC by HDL-C. The cholesterol retention fraction (CHOLDRF) was calculated as [(LDL-C - HDL-C)/LDL-C]. All blood samples were analyzed by LabCorp (Laboratory Corporation of America, Burlington, NC).

Statistical Analysis

For the purposes of statistical analysis, PFA scores were divided into three categories. Participants with PFA scores between 1 and 12 were categorized as walkers; those with PFA scores between 13 and 22 were categorized as joggers; and those with PFA scores between 23 and 26 were categorized as runners. These divisions were used as they appeared to be reasonable division points between the groups in order to reflect the differences between individuals in the groups.

All statistical analyses were produced using the statistical program R (R Development Core Team, 2010). Descriptive statistics for each of the variables were produced with particular concern over whether any of the measured variables showed significant differences across gender. Statistical differences across gender were only declared after computing a Bonfferroni correction factor for multiple tests. In an effort to search for patterns in the data, the correlation of each of the variables to cIMT was computed. These results (Tables 1,2 and 4) are reported without correction for multiple correlations. Finally, a multiple regression equation was

produced to predict cIMT from other variables of interest. First, an all subsets regression was performed using an exhaustive search algorithm as implemented in the 'regsubsets' command (Miller, 2002) in R. Using these results as a starting point, a number of models were examined in more detail. The reported model yielded the best R^2 and adjusted R^2 of all models examined.

Results

Table 1 includes various personal characteristics and their correlation to average cIMT. The men and women participating in this study were similar in age, resting blood pressure and hip circumference. As expected, men were significantly taller and heavier than their female counterparts. Independent of other variables, age, weight , waist and hip circumferences, WHR, and resting blood pressure were all significantly correlated to cIMT ($p<0.05$).

Table 2 shows the results of blood assays and the correlation of each component to cIMT. There were significant gender differences in TC, HDL-C, the TC/HDL ratio and the CHOLRF. HbA1C was significantly correlated to cIMT independent of other variables.

Table 3 shows differences in the same variables between participants categorized according to their self-reported PFA score. Due to the number of tests and inequality of group size, the *p*-values were not adjusted to maintain an alpha of 0.05. The uncorrected *p*-values are included in the table merely to show possible trends associated with the chosen physical activity level of participants. Given the above qualifications decreasing trends were apparent in average IMT, BMI, SBP, DBP, MAP, HbA1C and FBG between PFA categories (Table 3). Participants who self-reported lower (less active) PFA scores tended to have higher average IMT, BMI, blood pressure and FBG values.

All three indicators of physical activity and cardiorespiratory fitness were negatively correlated to cIMT, suggesting an inverse relationship between physical activity and cIMT (Table 4). Table 5 shows results of the regression analysis performed using cIMT as the dependent variable and all other variables of interest as independent variables. The multiple linear regression analysis yielded the following equation ($R^2 = 0.299$; Table 5) to estimate cIMT: 0.1286 + 0.00449(A) + 0.0337(G) + 0.00232(BMI) + 0.00108(SBP) + 0.000579(TC) - 0.000324(TRG), where: A is age in years, G is gender (0=female;1=male), BMI is body mass index (kg/m^2), SBP is systolic blood pressure (mmHg), TC is total cholesterol (mg/dL), and TRG is triglycerides (mg/dL). Each of the independent variables was significant ($p \leq 0.05$) in predicting VO$_2$max and the resulting regression equation accounted for roughly 30% (R^2=0.299) of the shared variance of measured cIMT. After accounting for these six variables, the other variables of interest that were independently correlated to cIMT (Tables 1 and 2), including the three primary measures of interest (predicted VO$_2$max, PFA, PA-R) were not significant.

Discussion

This study evaluated the relationship between cIMT and measures of physical activity, cardiorespiratory fitness, blood lipids, inflammation, blood glucose level, blood pressure, and anthropometric measures of obesity and central adiposity. The key findings of our study were that significant independent inverse correlations were found between PFA and predicted VO$_2$ max with cIMT, while PA-R was not significantly correlated to cIMT. The strongest predictors of cIMT, however, were age, gender, BMI, SBP, TC and TRG. All other correlations lost significance after accounting for these variables.

Previous studies have examined the relationship between calculated VO_2max and cIMT and have likewise found the relationship significant. (Ferreira, et al., 2003; Ferreira, Twisk, van Mechelen, Kemper, & Stehouwer, 2002; Lakka, et al., 2001)). Similar to our study Lakka, et al. showed significance was lost after the addition of multiple adjustments (Lakka, et al., 2001). The study included 854 Finnish men 42 to 60 years of age. VO_2max and cIMT were measured at baseline and again 4 years later. Measured VO_2max had a strong inverse correlation to 4-year increases in cIMT with adjustments made for age, technical covariates and cigarette smoking. However, after accounting for SBP, serum apolipoprotein B level, diabetes and plasma fibrinogen the association between measured VO_2max and cIMT was no longer statistically significant.

In our study, PA-R was not significantly correlated to cIMT (Table 4), even though PA-R has been used as a self-reported measure of physical activity and an independent variable in the prediction of VO_2peak (Heil, 1995; Jackson, et. al., 1990). We offer one explanation for why PA-R was not significantly correlated to cIMT. The recommended amount of physical activity for all Americans is 30 minutes of moderate intensity physical activity 5 days/week, 25 minutes of vigorous aerobic exercise 3 days/week, or some equal combination of moderate and vigorous physical activity that results in at least 500 to 1000 MET minutes per week. The PA-R is an 11-point scale that allows individuals to select an item that best describes their typical level of physical activity. Selecting items 0 through 5 on the PA-R scale indicate that weekly physical activity is less than 60 minutes and therefore does not meet the minimum recommended amount of weekly physical activity. The average self-reported PA-R for participants in this study was 5.2 (Table 4). Because the PA-R scale does not clearly differentiate intensity of exercise it may not be a good indicator of cardiovascular fitness. Although numerous health benefits are

associated with increasing levels of physical activity, there may be a stronger association between cardiovascular fitness and cIMT.

Only when no other independent variables were accounted for was PFA found to be significantly correlated to cIMT (Table 4). Participants were divided into 3 categories: walkers, joggers and runners, allowing trends between the groups to be seen (Table 3). Trends with increasing PFA categories include decreasing average cIMT, BMI, SBP, DBP, MAP, HBA1C and FBG. While little comparison has been made between PFA and cIMT, research has categorized subjects with an average age of 29 into endurance, recreational and non-athletes, somewhat similar to our three categories (Popovic, et al., 2010). Endurance athletes were defined as any person performing 3 or more hours of running and/or swimming and/or cycling consistently each week for at least 6 months. Recreational athletes were defined as any person performing 3 or more hours of general sports per week. The endurance and recreational athletes were combined for analysis and could be loosely compared to the runner and jogger groups in the present study. Non-athletes were any persons who did not meet the criteria to be included in the endurance or recreational athlete group. This group can be loosely compared to the walkers in the present study. Average cIMT was found to be about 0.49 mm which is lower than our study's cIMT value of about 0.74 mm (walkers) and 0.70 mm (joggers). This difference may be explained by the differences in age of the participants in our study (50 years of age and older) and the study by Popovic, et al. (20 to 40 years of age). Nevertheless, there were not significant differences in cIMT between groups in either the Popovic, et al. study or our study (Table 3).

It should also be considered that exercise and a person's physical activity level and cardiovascular fitness contribute to a person's improved CVD risk profile in many of the variables we assessed. Improving person's CVD risk profile is important and increased physical

activity is an established means of improving a person's profile of these risk factors. A cross sectional study found athletes to have a significantly lower BMI, relative body fat percent, waist circumference, cholesterol, LDL, TRG, CRPhs and leucocytes compared to non-athletes (Popovic, et al., 2010). Twelve weeks of exercise intervention significantly reduced body weight, fat mass, percent body fat, waist circumference, SBP, DBP, TC, LDL-C, fasting insulin, and CVD risk score and increased HDL-C (Jekal, et al., 2009). While the exercise intervention did not change cIMT, many CVD risk factors were improved. Baseline stratification of VO_2max into quartiles showed significant differences in BMI, WHR, SBP, DBP, LDL-C, HDL-C, TRG and fasting serum insulin as well as mean intensity of physical activity (MET) and mean cIMT (Lakka, et al., 2001). Thus, not only did CVD risk factors lessen with increasing VO_2max quartiles but cIMT improved and subjects were able to participate in physical activities of higher intensities. Other research has supported the association between increased physical activity and improved CVD risk factors (Moreau, et al., 2002; Van Roie et al., 2010).

Our secondary purpose was to determine which of the variables of interest were most predictive of cIMT. Variables such as age, gender, weight, waist circumference, hip circumference, WHR, SBP, DBP and MAP are widely accepted risk factors for cardiovascular disease (Crouse, et al., 1996; Jekal, et al., 2009; Lakka, et al., 2001; Luedemann, et al., 2002; Sato, et al., 2008; Schmidt-Trucksass, et al., 1999). In our study, many of these variables were significantly correlated to cIMT (Table 1). However, it is important to note that the variables most predictive of cIMT were age, gender BMI, SBP, TC, and TRG (Table 5); all other variables lost significance when accounting for these six variables.

The results of this study concur with the findings of previous research in that age and gender are significant predictors of cIMT (Crouse, et al., 1994; Lawlor, et al., 2004; Luedemann,

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et al., 2002; Schmidt-Trucksass, et al., 1999; Stein, et al., 2004; Tanaka, et al., 2002). The results of our study also concur with previous reports that men generally have a thicker cIMT compared to women (Lawlor, et al., 2004; Stein, et al., 2004). In the Bogalusa Heart Study, Stein, et al. (2004) studied 519 young adults with an average age of 32 years. Males had a significantly higher cIMT than their female counterparts. However, cIMT in post-menopausal women may exceed cIMT of men of equal age (Moreau, et al., 2002; Wildman, et al., 2004). Based on the age range of female participants in our study, we assume that many of the female participants were post-menopausal. Nevertheless, the women in our study had an average cIMT that was smaller (0.71 ± 0.09 mm) than that of the male (0.75 ± 0.11 mm) participants.

A BMI that is $\geq 30 kg/m^2$ is a risk factor for CVD for either gender. In our study BMI in and of itself was not significantly correlated to cIMT (Table 1). Other measures of central adiposity (i.e., waist and hip circumferences, WHR) were significantly correlated to cIMT (Table 1). Measures of central adiposity or body fat distribution increase the risk of CVD when waist circumference is >102 cm (40 inches) for men and >88 cm (35 inches) for women; BMI $\geq 30 kg \cdot m^2$ for both gender; and WHR >0.90 for men and >0.85 for women. In relation to cIMT Yan, et al. found WHR to be a more accurate measure of adiposity compared to BMI which may help explain why BMI was not significantly correlated to cIMT (Yan, et al., 2009). Yan et al. (2009) reported an association between cIMT and abdominal obesity as waist circumference, WHR and BMI varied significantly between quartiles of cIMT ($P <0.001$). In a four year follow up study of men 42 to 60 years of age, Lakka, et al. (2001) found WHR to be significantly correlated to 4-year increases in maximal cIMT but not significantly related to 4-year increases in mean cIMT.

The three remaining variables that were predictive of cIMT were SBP, TC, and TRG (Table 5). Systolic blood pressure ≥140 mmHg is a risk factor for CVD (Thompson, 2010). The results of our study concur with previous studies reporting the correlation between SBP and cIMT (Jekal, et al., 2009; Lakka, et al., 2001; Luedemann, et al., 2002; Sato, et al., 2008; Schmidt-Trucksass, et al., 1999; Yan, et al., 2009). A total cholesterol ≥200 (mg·dL^{-1}) is a risk factor of CVD (Thompson, 2010). Previous research has also found a correlation between cIMT and total cholesterol (Jekal, et al., 2009; Luedemann, et al., 2002; Schmidt-Trucksass, et al., 1999; Yan, et al., 2009). High TC levels are commonly treated with medication, changes in diet and through increased exercise and physical activity, especially in individuals with elevated risk of CVD. Numerous studies have indicated the beneficial effect of lowering blood lipid levels in order to lower risk of CVD (Jekal, et al., 2009; Luedemann, et al., 2002; Schmidt-Trucksass, et al., 1999; Yan, et al., 2009). The final variable which was included in the model to predict cIMT was TRG. TRG is not a risk factor for CVD as defined by ACSM but may predispose a person to CVD; TRG is considered borderline high when ≥150 (mg·dL^{-1}) and high when ≥200 (mg·dL^{-1}) (Thompson, 2010). Research is inconclusive on the association between TRG and cIMT. One study divided cIMT into quartiles and found TRG levels to be significantly different between the groups (Yan, et al., 2009) but other researchers found no significant correlation (Jekal, et al., 2009; Schmidt-Trucksass, et al., 1999). Lowering of elevated TRG levels is a concern for individuals with increased risk of CVD and is often treated with changes in lifestyle including diet and exercise and with the use of medication. Thus, these modifiable risk factors of SBP, TC, and TRG are improved with increased physical activity and exercise which likely contributes to a smaller cIMT.

The regression model presented in this study (Table 5) confirms the association of modifiable risk factors such as TC, SBP, BMI, and TRG with the development and progression of CVD, as indicated by increase of cIMT. The regression model explains only 30% of the variance in cIMT in this group of participants. Another study found age, hyperlipidemia cigarette smoking, type 2 diabetes, hypertension and coronary artery disease to be most predictive of cIMT (adjusted $R^2 = 0.371$ in women; adjusted $R^2 = 0.276$ in men) (Kablak-Ziembicka, et al., 2005). While several variables in this regression equation are different than our study the R^2 values are fairly consistent. Although all potential variables were included in our regression analysis, the model did not include other important CVD risk factors that may contribute to increased cIMT, such as cigarette smoking or genetic and family history of CVD. Research predominantly supports a link between cigarette smoking and cIMT (Kablak-Ziembicka, et al., 2005; Lakka, et al., 2001; Luedemann, et al., 2002; Yan, et al., 2009) and a genetic or family history component to cIMT (Lavrencic, Kosmina, Keber, Videcnik, & Keber, 1996; Sacco, et al., 2009). Adding these variables may help strengthen our R^2, however, cigarette smoking was a component in the above regression model resulting in a comparable R^2 value. Inclusion of additional potential variables in the model (from Tables 1,2 and 4) did not improve the model. It is likely that many of the variables are inter-related, making it difficult to account for the influence of each independent variable.

This study is not without limitations. The results of this study may not be inferred to the entire senior population. The participants at the HWSG represent a convenient sample of physically active men and women over 50 years of age. This study used self-reported physical activity ratings (i.e., PA-R) and perceived fitness levels (i.e., PFA) as measures of physical activity. Self-reporting always introduces potential sources of error but is a viable alternative

when direct measures of physical activity are not feasible. The use of the PA-R and PFA

represent an alternative and novel approach to evaluating the association between physical

activity and cIMT in large sample sizes.

Conclusion

This study investigated the relationship between physical activity and cardiorespiratory

fitness to cIMT and CVD risk factors in seniors at the HWSG. Of the primary variables of

interest, predicted VO_2max, and PFA were significantly correlated to cIMT before accounting

for other variables, but they were not significant independent variables in the regression model to

predict cIMT. Our regression analysis indicated that age, gender, BMI, SBP, TC, and TRG were

the most important variables of interest to predict cIMT in physically active seniors participating

in the HWSG. We conclude that physical activity and cardiorespiratory fitness have an indirect

impact on cIMT through its influence on the modifiable risk factors for CVD we identified in our

regression analysis.

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Table 1. Personal Characteristics Correlated to Carotid Artery IMT

	Male (n = 199)	Female (n = 142)	Combined (n = 341)	Correlation to IMT (r)	Confidence Interval	p-value
Age (years)	68.4 ± 7.9	66.4 ± 8.5	67.6 ± 8.2	0.4258	0.33–0.51	< 0.001†
Height (m)*	1.7 ± 0.07	1.6 ± 0.08	1.71 ± 0.1	0.0962	−0.01–0.20	0.077
Weight (kg)*	84.1 ± 13.8	67.0 ± 12.4	77.04 ± 15.7	0.1108	0.00–0.21	0.042†
BMI (kg/m^2)*	26.7 ± 3.8	25.4 ± 4.7	26.15 ± 4.3	0.0738	−0.03–0.18	0.176
Waist (cm)*	96.9 ± 10.5	83.3 ± 12.5	91.26 ± 13.2	0.1678	0.06–0.27	0.002†
Hip (cm)	104.1 ± 7.4	101.9 ± 9.5	103.2 ± 8.4	0.1072	0.00–0.21	0.048†
Waist-hip ratio (WHR)*	0.93 ± 0.06	0.82 ± 0.07	0.88 ± 0.09	0.1668	0.06–0.27	0.002†
Systolic blood pressure (mmHg)	135.2 ± 18.2	130.6 ± 20.1	133.3 ± 19.1	0.3392	0.24–0.43	< 0.001†
Diastolic blood pressure (mmHg)	79.8 ± 9.9	79.2 ± 10.7	79.5 ± 10.2	0.1320	0.02–0.23	0.017†
Mean Arterial Pressure (mmHg)	98.3 ± 11.9	96.3 ± 12.8	97.4 ± 12.3	0.2486	0.14–0.34	< 0.001†
Average cIMT (mm)*	0.75 ± 0.11	0.71 ± 0.09	0.73 ± 0.10			

All values are mean ± standard deviation. *Significant gender differences ($p < 0.05$) in values after correction for multiple tests. †Significant difference between variable and cIMT ($p < 0.05$) without correction for multiple tests. All correlations are for the combined group (n=341).

Table 2. Blood Characteristics Correlated to Carotid Artery IMT

	Male (n = 197)	Female (n = 142)	Combined (n = 339)	Correlation to IMT (r)	Confidence Interval	p-value
Total Cholesterol (TC) (mg/dL)*	186.95 ± 35.2	203.62 ± 37.2	193.94 ± 36.9	0.743	−0.03–0.18	0.172
HDL-Cholesterol (HDL) (mg/dL)*	56.87 ± 12.6	70.57 ± 20.0	62.51 ± 17.5	0.0075	−0.09–0.11	0.890
LDL-Cholesterol (LDL) (mg/dL)	110.55 ± 32.3	112.97 ± 32.2	111.57 ± 32.2	0.0972	−0.01–0.20	0.074
VLDL-Cholesterol (VLDL) (mg/dL)	19.66 ± 10.5	20.62 ± 11.2	20.06 ± 10.8	−0.0573	−0.16–0.05	0.293
Triglycerides (TRG) (mg/dL)	99.99 ± 58.1	102.20 ± 56.7	100.92 ± 57.5	−0.0752	−0.18–0.03	0.167
hs-CRP (mg/dL)	2.24 ± 2.6	2.25 ± 2.3	2.24 ± 2.4	0.0421	−0.06–0.14	0.439
HbA1C(%)	5.76 ± 0.6	5.72 ± 0.37	5.74 ± 0.4	0.1605	0.05–0.26	0.003†
Fasting Blood Glucose (FBG) (mg/dL)	92.74 ± 19.6	88.74 ± 12.7	91.06 ± 17.2	0.0972	−0.01–0.20	0.074
TCHDL Ratio£*	3.42 ± 0.9	3.07 ± 0.9	3.27 ± 0.9	0.0365	−0.07–0.14	0.503
CHOLRF§*	0.45 ± 0.19	0.36 ± 0.21	0.41 ± 0.2	0.0613	−0.04–0.16	0.260

All values are mean ± standard deviation. *Significant gender differences ($p < 0.05$) in values after correction for multiple tests. †Significant difference between variable and cIMT ($p < 0.05$) without correction for multiple tests. All correlations are for the combined group (n=339). §Cholesterol retention fraction (CHOLDRF) was calculated as [(LDL-C - HDL-C)/LDL-C]. £Total cholesterol/ HDL cholesterol (TCHDL) ratio was calculated by dividing TC / HDL-C

Table 3. Personal Characteristics by PFA Levels

	Walker (PFA 0–12) (n = 243)	Jogger (PFA 13–22) (n = 87)	Runner (PFA > 23) (n = 5)	p value
Average cIMT (mm)	0.74 ± 0.1	0.72 ± 0.1	0.70 ± 0.09	0.3068
BMI (kg/m^2)	26.68 ± 4.4	24.81 ± 3.6	23.96 ± 2.3	0.0012†
Waist-hip ratio (WHR)	0.88 ± 0.08	0.87 ± 0.07	0.89 ± 0.06	0.3388
Systolic blood pressure (SBP) (mmHg)	133.67 ± 18.9	131.82 ± 19.3	121.00 ± 23.9	0.3133
Diastolic blood pressure (DBP) (mmHg)	79.87 ± 10.3	78.52 ± 9.6	73.60 ± 13.7	0.2705
Mean Arterial Pressure (MAP) (mmHg)	97.80 ± 12.2	96.3 ± 12.1	89.33 ± 17.1	0.2441
Total Cholesterol (TC) (mg/dL)	193.93 ± 38.3	194.49 ± 33.4	202.00 ± 35.8	0.8718
HDL-Cholesterol (HDL) (mg/dL)	61.5 ± 17.2	65.8 ± 17.9	60.6 ± 20.6	0.1610
LDL-Cholesterol (LDL) (mg/dL)	111.4 ± 32.3	112.2 ± 30.2	109.2 ± 63.4	0.9634
VLDL-Cholesterol (VLDL) (mg/dL)	21.1 ± 11.2	16.5 ± 6.9	32.2 ± 25.0	0.0001†
Triglycerides (TRG) (mg/dL)	106.7 ± 60.4	81.0 ± 35.4	161.8 ± 125.2	0.0001†
hs-CRP (mg/dL)	2.4 ± 2.5	1.6 ± 1.8	4.5 ± 5.0	0.0361†
HbA1C(%)	5.7 ± 0.4	5.6 ± 0.4	5.5 ± 0.2	0.0107†
Fasting Blood Glucose (FBG) (mg/dL)	91.7 ± 18.0	89.9 ± 14.8	77.6 ± 12.1	0.1533
TCHDL Ratio£	3.3 ± 0.9	3.1 ± 0.8	3.7 ± 1.8	0.1019
CHOLRF§	0.41 ± 0.20	0.39 ± 0.20	0.46 ± 0.29	0.5177

All values are mean ± standard deviation. †P-value tests null hypothesis that all three groups (Walker, Jogger, Runner) are the same ($p < 0.05$). There is no correction for multiple tests §Cholesterol retention fraction (CHOLDRF) was calculated as [(LDL-C - HDL-C)/LDL-C]. £Total cholesterol/ HDL cholesterol (TCHDL) ratio was calculated by dividing TC / HDL-C

Table 4. Physical Activity Measurements Correlated to Carotid Artery IMT

	Male (n = 199)	Female (n = 142)	Combined (n = 341)	Correlation to IMT (r)	Confidence Interval	p-value
PA-R Score	5.2 ± 2.4	5.1 ± 2.4	5.1 ± 2.4	-0.0869	$-0.19 - 0.02$	0.111
PFA Score	10.7 ± 5.6	8.8 ± 4.9	9.9 ± 5.4	-0.1359	$-0.24 - -0.03$	0.012†
Predicted VO$_2$max (mL·kg^{-1}·min^{-1})	32.2 ± 6.8	25.8 ± 7.4	29.6 ± 7.7	-0.1475	$-0.25 - -0.04$	0.007†
Average cIMT (mm)	0.75 ± 0.11	0.72 ± 0.09	0.73 ± 0.10			

All values are mean ± standard deviation. *Significant gender differences ($p < 0.05$) in values after correction for multiple tests. †Significant difference between variable and cIMT ($p < 0.05$) without correction for multiple tests. All correlations are for the combined group (n=341).

Table 5. Regression Analysis of Independent Variables and Carotid Artery IMT

	Estimate	*t*-value	*p* value
Intercept	0.1286	2.061	0.04
Age	0.00449	7.166	< 0.001
Gender	0.0337	3.310	0.001
BMI (kg/m^2)	0.00232	1.892	0.05
Systolic Blood Pressure	0.00108	3.952	< 0.001
Total Cholesterol	0.000579	4.184	<0.001
Triglycerides	−0.000324	−3.466	< 0.001

Multiple R^2= 0.299. The resulting prediction equation for cIMT is 0.1286 + 0.00449(A) + 0.0337(G) + 0.00232(BMI) + 0.00108(SBP) + 0.000579(TC) - 0.000324(TRG), where: A is age in years, G is gender (0=female;1=male), BMI is body mass index (kg/m^2), SBP is systolic blood pressure (mmHg), TC is total cholesterol (mg/dL), and TRG is triglycerides (mg/dL).

Appendix A

Instructions: Please complete all information on the front and back side of this page.

_____   _____ Date of Birth _____ / _____ / _____
First Name   Last Name   month / day / year

_____   ☐ Male   ☐ Single – Never married or divorced
                      ☐ Female   ☐ Married – Spouse is deceased
Age   ☐ Married – Spouse is living

☐ Caucasian (white)   ☐ African American   ☐ African- Other   ☐ Hispanic / Latino

☐ American Asian   ☐ Pacific Islander   ☐ American Indian   ☐ Other _____

_____
Email Address

_____   _____
Home Phone Number   Cell Phone Number

(Results will be sent to you by email. If we have problems sending you your results by email, we will contact you by phone to verify your email address).

In which sport are you participating in this year?
If you are participating in more than one sport, select the one that you consider your preferred or most dominant sport.

☐ Archery   ☐ Racewalk
☐ Badminton   ☐ Racquetball
☐ Basketball   ☐ Road Race
☐ Bowling   ☐ Shooting
☐ Bridge   ☐ Soccer
☐ Cowboy Action Shooting   ☐ Softball
☐ Cycling   ☐ Square Dancing
☐ Golf   ☐ Swimming
☐ Horseshoes   ☐ Table Tennis
☐ Lawn Bowls   ☐ Tennis
☐ Mountain Biking   ☐ Track and Field
☐ Pickleball   ☐ Triathlon
                                 ☐ Volleyball

☐ None (Guest)

Answer each question by checking either the **YES** or **NO** box. If you are uncertain, skip the question.

Yes No

☐ ☐ Do you have a father or brother who had a heart attack or heart surgery before the age of 55 or a mother or sister who had a heart attack or heart surgery before the age of 65?
☐ ☐ Do you smoke now or have you quit smoking in the last 6 months?
        If you currently smoke, how many packs per week do you smoke? _____ packs/week
☐ ☐ Do you get <u>less</u> than 30 minutes of moderate-intensity physical activity during three or more days per week?
☐ ☐ Do you take medications to control your blood pressure?
☐ ☐ Do you take medications to control your cholesterol?
☐ ☐ Do you have chest pain during physical activity or exercise?
☐ ☐ Do you have chest pain at rest or doing usual activities?
☐ ☐ Do you experience unusual shortness of breath when resting or with usual activities of daily living?
☐ ☐ Do you have shortness of breath during physical activity or exercise?
☐ ☐ Do you have difficulty breathing when reclined, lying down or sleeping?.
☐ ☐ Do you experience dizziness, fainting, or blackouts?
☐ ☐ Do you have swelling of the ankles?
☐ ☐ Do you have (or have you had) sensations of a rapid or irregular heart beat?
☐ ☐ Do you have burning or cramping sensations in your legs when walking?
☐ ☐ Do you lose consciousness or balance because of dizziness?

Do you have any of the following (check all that apply)?
Yes No
☐ ☐ Cardiovascular disease
☐ ☐ Coronary heart disease
☐ ☐ Heart murmur
☐ ☐ Heart valve disease
☐ ☐ Hypertension
☐ ☐ Pacemaker
☐ ☐ Kidney disease
☐ ☐ Liver disease
☐ ☐ Diabetes
☐ ☐ Thyroid disorder
☐ ☐ Pulmonary disease such as asthma, cystic fibrosis, interstitial lung disease, or COPD

Have you ever had any of the following (check all that apply)?
Yes No
☐ ☐ Heart attack
☐ ☐ Stroke
☐ ☐ Any kind of heart surgery, including catherization, stents, angioplasty, bypass, ablation, or valve replacement

Are you currently taking any prescription medications?
Yes No
☐ ☐ For what?
_____

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☐ Blood Draw Completed
☐ Permission to Contract

_____ _____
Name   ID

Height   _____ in   Weight: _____ pds

Waist Circumference   _____ in   Hip Circumference   _____ in

Body Fat   _____ %

Resting Blood Pressure: _____ / _____

Right Carotid Artery   Anterior View   _____

                          Direct View   _____

                          Posterior View   _____   Average Right IMT   _____

Left Carotid Artery   Anterior View   _____

                          Direct View   _____

                          Posterior View   _____   Average Left IMT   _____

                                                                         Combined Avg IMT   _____

Appendix B

PHYSICAL ACTIVITY RATING

INSTRUCTIONS
CIRCLE the one number (0 – 10) that <u>best</u> <u>describes</u> your typical level of physical activity over the previous 6 MONTHS:

0 =   avoid walking or exertion; e.g., always use elevator, drive when possible instead of walking

1 =   **LIGHT ACTIVITY:** walk for pleasure, routinely use stairs, occasionally exercise sufficiently to cause heavy breathing or perspiration

2 =   **MODERATE ACTIVITY:** 10 to 60 minutes per week of moderate activity; such as golf, horseback riding, calisthenics, table tennis, bowling, weight lifting, yard work, cleaning house, walking for exercise

3 =   **MODERATE ACTIVITY:** over 1 hour per week of moderate activity as described above

4 =   **VIGOROUS ACTIVITY:** run less than 1 mile per week or spend less than 30 minutes per week in comparable activity such as running or jogging, lap swimming, cycling, rowing, aerobics, skipping rope, running in place, or engaging in vigorous aerobic-type activity such as soccer, basketball, tennis, racquetball, or handball

5 =   **VIGOROUS ACTIVITY:** run 1 mile to less than 5 miles per week or spend 30 minutes to less than 60 minutes per week in comparable physical activity as described above

6 =   **VIGOROUS ACTIVITY:** run 5 miles to less than 10 miles per week or spend 1 hour to less than 3 hours per week in comparable physical activity as described above

7 =   **VIGOROUS ACTIVITY:** run 10 miles to less than 15 miles per week or spend 3 hours to less than 6 hours per week in comparable physical activity as described above

8 =   **VIGOROUS ACTIVITY:** run 15 miles to less than 20 miles per week or spend 6 hours to less than 7 hours per week in comparable physical activity as described above

9 =   **VIGOROUS ACTIVITY:** run 20 to 25 miles per week or spend 7 to 8 hours per week in comparable physical activity as described above

10 =   **VIGOROUS ACTIVITY:** run over 25 miles per week or spend over 8 hours per week in comparable physical activity as described above

PERCEIVED FUNCTIONAL ABILITY

INSTRUCTIONS: CIRCLE the single number (1–13) that best represents your response to the following question.

1   Suppose you were going to exercise continuously on an indoor track for 1 mile. Which exercise pace is just right for you, meaning <u>not too easy</u> and <u>not too hard</u>?

   1   WALKING at a *slow* pace (18 minutes per mile or more)
   2
   3   WALKING at a *medium* pace (16 minutes per mile)
   4
   5   WALKING at a *fast* pace (14 minutes per mile)
   6
   7   JOGGING at a *slow* pace (12 minutes per mile)
   8
   9   JOGGING at a *medium* pace (10 minutes per mile)
   10
   11   JOGGING at a *fast* pace (8 minutes per mile)
   12
   13   RUNNING at a *fast* pace (7 minutes per mile or less)

INSTRUCTIONS: CIRCLE the single number (1–13) that best represents your response to the following question.

2   Suppose you were going to exercise continuously on an indoor track for 3 miles. Which exercise pace is just right for you, meaning you do NOT become breathless or overly fatigued? Be realistic.

   1   I could WALK the entire distance at a *slow* pace (18 minutes per mile or more)
   2
   3   I could WALK the entire distance at a *medium* pace (16 minutes per mile)
   4
   5   I could WALK the entire distance at a *fast* pace (14 minutes per mile)
   6
   7   I could JOG the entire distance at a *slow* pace (12 minutes per mile)
   8
   9   I could JOG the entire distance at a *medium* pace (10 minutes per mile)
   10
   11   I could JOG the entire distance at a *fast* pace (8 minutes per mile)
   12
   13   I could RUN the entire distance at a *fast* pace (7 minutes per mile or less)

CORRELATION OF CAROTID ARTERY INTIMA-MEDIA THICKNESS AND SPORT PARTICIPATION BASED ON

METABOLIC EQUIVALENT VALUES IN SENIORS

by

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Chapter 1

Introduction

Cardiovascular disease (CVD) is the most prevalent cause of death in the United States (Cobble & Bale, 2010). Atherosclerosis is the most threatening form of heart disease, a major form of CVD, and is responsible for 50% of deaths in the country (Lusis, 2000). Atherosclerosis is the buildup of lipoproteins, foam cells, smooth muscle cells and necrotic tissue in blood vessel walls, specifically, in the arterial lumen and between the intima and media layers of arteries. Atherosclerotic material is often referred to as plaque. There are two risks associated with atherosclerotic plaque: hemodynamically significant lessions which restrict blood flow, and thromboembolic plaque which can dislodge small clots into the circulation. Plaque can cause cardiovascular events such as myocardial infarction and stroke. A person's CVD risk increases greatly as atherosclerosis progresses.

One way to evaluate the atherosclerotic burden, or the progression of atherosclerosis, is to measure the thickness of the intima and media layers of the arteries. This can be done non-invasively using Doppler ultrasound. The carotid arteries are the vessels of choice to measure the intima-media thickness (IMT) because of the ease at which they can be imaged. Sonography of the carotid arteries is accurate, reliable, inexpensive and harmless to the subject after repeated measurements (Cobble & Bale, 2010; Stein, et al., 2008). The benefit of sonographic measures of the carotid artery IMT is that it allows early detection of atherosclerosis, long before adverse symptoms are manifest (Cobble & Bale, 2010). Carotid IMT is an important tool which can successfully predict future cardiovascular events (Chambless, et al., 1997; Lorenz, Markus, Bots, Rosvall, & Sitzer, 2007; O'Leary, et al., 1999; Schmidt, Fagerberg, & Hulthe, 2005; Wyman, Mays, McBride, & Stein, 2006). Carotid artery IMT is used both clinically and in research to measure lifestyle and therapeutic intervention associated atherosclerotic changes over time (Cobble & Bale, 2010).

Since a thickening of the carotid artery IMT is used to measure the progression of atherosclerosis, a decrease in the carotid artery IMT suggests a decrease in a person's risk of CVD. Research generally supports a decrease in the carotid artery IMT with increasing levels of physical activity and exercise. For example, aerobic exercise in women increased blood high density lipoprotein (HDL) levels and decreased harmful low density lipoproteins (LDL) (Eapen, 2009; Kelley, 2005). Endurance exercise slowed the progression of IMT in menopausal women (Moreau, et al., 2002; Stein, et al., 2008; Wildman, Schott, Brockwell, Kuller, & Sutton-Tyrrell, 2004). Vigorous activity decreased carotid IMT after three years (Kozakova, et al.). Walking 4-5 km/day retarded the progression of carotid artery IMT in subjects with CHD (Sato, Makita, Uchida, Ishihara, & Majima, 2008). However, two studies failed to show a correlation between physical activity and carotid artery IMT. In one study, endurance and recreational exercise was correlated to decreased risk factors for CVD, however there were no differences in carotid artery IMT when compared to a sedentary group (Popovic, et al.). In a two-part cross-sectional and 3 month aerobic exercise intervention study exercise failed to decrease carotid artery IMT (Tanaka, et al., 2002), however, 3 months may not have been long enough to cause an affect. In summary, carotid artery IMT has been studied in relation to various intensities of exercise in various ages in both healthy individuals and individuals with cardiovascular disease. While the relationship between exercise and carotid artery IMT has been studied, there is a paucity of research on sports participation and the influence individual sports have on carotid artery IMT.

Research indicates that carotid artery IMT increases with both age and menopause (Anjan K. Sinha, 2002; Kablak-Ziembicka, et al., 2005; Sutton-Tyrrell, 1998), thus seniors are most at risk of CVD. However, although people who are 50 years of age and older could benefit from increased levels of physical activity, they tend to be less active than their younger counterparts (Hooker, et al., 2005). Many seniors may not prefer repetitive, endurance activity and may be unable to participate in vigorous activity. However, many sports and recreational activities such as golf, tennis, racquetball and softball

may be enjoyable for seniors. Recreational activity, as a single broad category of activities (rather than specific individual sports) has been studied in young adults (Popovic, et al.). The impact of sports participation on carotid artery IMT has not been studied in seniors. The annual Huntsman World Senior Games (HWSG) in St. George is a venue that encourages physical activity and sports participation (and competition) in seniors aged 50 years and older. The energy expenditure of each of the sports included in the HWSG can be categorized by energy expenditure using the Compendium of Physical Activity (or similar resources)(Ainsworth, 2002). Examining the influence of sports participation at the HWSG on carotid artery IMT can be a valuable tool to evaluate the relationship between various forms of exercise (and energy expenditure) and carotid artery IMT in seniors.

Statement of Purpose

The purpose of this study is to evaluate the relationship between carotid artery IMT and participation in various sports requiring a wide range of energy expenditure in senior males and females.

Research Hypothesis

Carotid artery IMT is influenced by the sport in which a senior competes. There will be an inverse relationship between energy expenditure and carotid artery IMT values.

Null Hypothesis

There is no correlation between carotid artery IMT and the energy expenditure of the sport in which a senior competes.

Definition of Terms

Atherosclerosis – Also known as arteriosclerosis. Applied to a number of conditions in which there are thickening, hardening and loss of elasticity of the walls of arteries. Marked by cholesterol-lipid-calcium deposits in the walls of arteries restricts blood flow (F. A. Davis, 2009).

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Body mass index (BMI) – An index used to assess weight (kg) relative to height (m²). Normal BMI is <25 kg/m^2. Overweight is defined as ≥25 kg/m^2 and <30 kg/m^2. Obesity is defined as ≥30 kg/m^2 (Walter R. Thompson, 2010)

Cardiovascular disease (CVD) - Disease of the heart or blood vessels (F. A. Davis, 2009).

Coronary heart disease (CHD) – Decrease blood flow to the heart muscle to the extent that either basal needs for oxygen are unmet or the oxygen supply is insufficient when an increased demand for oxygen is made, as in work. This cause is usually due to atherosclerosis of coronary arteries; any other factor limiting blood flow through these arteries may be involved. The end result is temporary or permanent damage to the heart (F. A. Davis, 2009).

High risk carotid artery IMT – Measured thickness of the carotid artery IMT ≥1 mm or a carotid artery IMT that is greater than the 75th percentile for a person's age, sex and race. Plaque stenosis is less than 50%. (Cobble & Bale, 2010; Stein, et al., 2008)

Intima-media thickness (IMT) – The intima, or intimal, is the innermost coat of a blood vessel. The media is the middle or muscular coat of an artery. The thickness of these two layers is the intima-media thickness (F. A. Davis, 2009).

Lipoproteins – Conjugated proteins consisting of simple proteins combined with lipid components: cholesterol, phospholipid and triglyceride. Most plasma lipids do not circulate in an unbound state but are chemically linked with proteins. These large molecules are categorized by their chemical properties and densities as determined by ultracentrifugation. More dense molecules are linked with more proteins. Lipoproteins are classified as very low density (VLDL), low-density (LDL), and high-density (HDL). Individuals with high levels of HDL are less predisposed to CHD (F. A. Davis, 2009).

Moderately high risk carotid artery IMT – Measured thickness of the carotid artery IMT that is <1 mm and in the 50th-75th percentile for a person's age, sex and race. No plaques present. (Cobble & Bale, 2010; Stein, et al., 2008)

Myocardial infarction (MI) – Condition caused by partial or complete occlusion of one or more of the coronary arteries, commonly referred to as a heart attack (F. A. Davis, 2009).

Plaque – A yellow swollen area of the lining of an artery. It is formed by accumulation of lipids in the area. Mannheim Intima-Media Thickness Consensus Panel clinically defines plaque as an isolated carotid artery IMT of ≥1.5 mm or a catorid artery IMT larger than 50% of the surrounding IMT. Some physicians consider plaque to be anything equal to or larger than a maximal IMT of 1 mm (Cobble & Bale, 2010; Stein, et al., 2008).

Senior – An individual who is 50 or more years of age ("Huntsman World Senior Games," 2010).

Stroke – Sudden loss of consciousness followed by paralysis caused by one of several different mechanisms including hemorrhage into brain; formation of an embolus or thrombus that occludes an artery; or rupture of an extracerebral artery causing subarachnoid hemorrhage (F. A. Davis, 2009).

Very high risk carotid artery IMT - Measured thickness of the carotid artery IMT that is ≥1 mm or a carotid artery IMT that is greater than the 75th percentile for a person's age, sex and race. Plaque stenosis will be greater than or equal to 50%. (Cobble & Bale, 2010; Stein, et al., 2008)

Assumptions

The following assumptions apply to this study:

- Participants accurately recall and report how long they have routinely participated in the sport they are competing in.
- Participants play the sport they are competing in more than any other of sport.

Delimitations

Participants in this study will be limited to seniors over the age of 50 years competing in events at the 2010 St. George Huntsman World Senior Games.

Limitations

Intensity and duration of sport participation is not documented along with years of participation

in sport of choice.

Chapter 2

Review of Literature

Nearly 80 million people in the United States are afflicted with cardiovascular disease (CVD) making it the number one killer in the country (Cobble & Bale, 2010). CVD includes any disease affecting the heart or vascular system. According to the American Heart Association (AHA), the four most common types of CVD are coronary heart disease (CHD) (including heart attacks and angina pectoris), stroke, high blood pressure (hypertension) and heart failure. While many diseases are unpreventable or even curable, CVD can often be avoided and successfully treated especially if detected early in development. Early detection of CVD involves screening and identifying r risk factors of the disease or recognizing an increased chance of developing CVD.

Risk Factors of CVD

The American College of Sports Medicine (ACSM) has defined eight positive risk factors that increase a person's risk for having cardiovascular, pulmonary or metabolic disease (Popovic, et al.):

1. Age. Men ≥45 years, Women ≥55 years

2. Family history. Myocardial infarction (MI), coronary revascularization, or sudden death before 55 years of age in father or other male first degree relative or before 65 years of age in mother or other female first degree relative.

3. Cigarette smoking. Current smoker or those who quit within the previous 6 months or have been exposed to environmental tobacco smoke.

4. Sedentary lifestyle. Not participating in at least 30 minutes of moderate intensity (40%-60% VO_2R) physical activity on at least three days a week for at least three months.

5. Obesity. Body mass index ≥30 kg·m² or waist girth >102cm for men and >88 cm for women.

6. Hypertension. Systolic blood pressure ≥140 mmHg and/or diastolic ≥90 mmHg confirmed at least twice on separate occasions or taking antihypertensive medication.

7. Dyslipidemia. Low-density lipoprotein cholesterol ≥130 mg/dL or high-density lipoprotein cholesterol <40mg/dL or on lipid-lowering medication. If total serum cholesterol is all that is available then it should be <200 mg/dL.

8. Prediabetes. Impaired fasting glucose equal to fasting plasma glucose ≥100mg/dL or impaired glucose tolerance equal to 2-hour values in oral glucose tolerance test ≥140mg/dL, confirmed at least twice on separate occasions.

High-serum HDL cholesterol ≥60 mg/dL acts as a negative risk factor, meaning it cancels out one positive risk factor.

There are different risk stratifications as defined by the ACSM: low, moderate and high. Individuals at low risk have one or less of the above risk factors and no symptoms of disease. Individuals at moderate risk have two or more of the above risk factors but no symptoms of disease. Individuals at high risk have known cardiovascular, pulmonary or metabolic disease or have one or more sign or symptom of CVD (Popovic, et al.). As a person's risk stratification increases so does their likelihood of developing CVD.

Atherosclerosis

Atherosclerosis is a subcategory of CVD and is characterized by an accumulation of lipids and fibrous elements in large arteries. It is the primary cause of heart disease and alone accounts for about 50% of all deaths in westernized societies (Lusis, 2000). Many studies show atherosclerosis as a risk factor or a valuable predictive tool for MI, stroke and other cardiovascular events (Kitamura, et al., 2004; O'Leary, et al., 1999; Schmidt, et al., 2005; Wyman, et al., 2006). Atherosclerosis is a progressive disease that begins in childhood and progresses over a person's lifetime, throughout which, different stages or severities of atherosclerotic lesions can develop increasing a person's chance of cardiovascular events.

To understand the various stages of atherosclerosis, it is requisite that basic artery anatomy is known. The wall of any artery is composed of three layers (Figure 1). The tunica-intima is the very thin

inner-most layer which borders the lumen of the vessel. It consists of a layer of endothelial cells over a basement membrane. The second (middle) layer is the tunica-media which is composed of smooth muscle and connective tissue arranged circumferentially around the vessel. The smooth muscle cells of the tunica-media contract or relax, causing constriction or dilation, respectively, of the artery. The tunica-externa (or adventitia) is the third (outermost) layer which is composed mostly of connective tissue with intermingling fibroblasts and smooth muscles cells (Lusis, 2000) arranged longitudinally with the vessel. The thickness of each layer and its composition varies slightly with the size of the artery. The distance between the lumen/tunica-intima border and the tunica-media/tunica-externa border is called IMT.

Stages of Atherosclerosis

There are five stages in development of atherosclerosis: lesion initiation, inflammation, foam-cell formation, formation of fibrous plaques and complex lesions and thrombosis (Lusis, 2000).

Lesion Initiation

The first stage of atherosclerosis is LDL accumulation in the subendothelial intima matrix. Endothelial cells, the innermost cells of an artery, are tubular shaped and align in the direction of blood flow. Where an artery bends or branches blood flow is disturbed and endothelial cells are polygonal shaped and don't have a particular orientation. In these areas of bending or branching macromolecules such as LDL can more easily pass through endothelial gap junctions and become trapped in the subendothelial matrix, or intima layer. This entrapment of LDL happens early in life; 45 percent of infants up to eight months of age show signs of lipid retention (Fuster, Badimon, Badimon, & Chesebro, 1992). This buildup is greater with increased blood low-density lipoprotein (LDL) levels. LDL undergoes oxidation while trapped in the intima through interaction with reactive oxygen species (ROS). High-density lipoprotein (HDL) strongly protects against atherosclerosis by removing excess LDL from peripheral tissues and inhibiting LDL oxidation.

Inflammation

Inflammation causing molecules like lymphocytes, monocytes and macrophages are attracted to lesions through minimally oxidized lipoproteins. Oxidized LDL stimulates endothelial cells to produce pro-inflammatory molecules including adhesion molecules, chemotactic proteins and growth factors like macrophage colony-stimulating factor (M-CSF). This leads to increased recruitment of monocytes and lymphocytes in the vessel wall. Besides being oxidized, lipoproteins may also be modified through lipolysis, proteolysis and aggregation which may also recruit white blood cells (WBCs). Oxidized LDL also inhibits the production of nitric oxide (Lusis, 2000), a vasodilator released by endothelial cells. Smaller vessels mean more shear stress and possible inflammation. Oxidized LDL leads to inflammation through attracting monocytes and lymphocytes and decreasing blood vessel diameter.

Foam Cell Formation

Foam cells are cholesterol engorged macrophages formed if LDL is extensively modified, or highly oxidized. Macrophages are a differentiated monocyte attracted to lesions by oxidized LDL. They engulf and digest material the cell doesn't want, thus, they consume lipoproteins. When the lipoproteins are sufficiently oxidized macrophages engulf LDL so quickly they become engorged foam cells. Foam cells release apolipoprotein E (apoE) which assists in the removal of excess cholesterol. When foam cells die they leave behind a mass of extracellular lipids and other cellular debris it engulfed. In working towards decreasing intima lipoproteins macrophages end up leaving behind a lipid mess that enhances atherosclerotic progression.

Formation of Fibrous Plaques

Fibrous plaques are characterized by a growing mass of extracellular lipids, mostly cholesterol and its ester, and accumulation of smooth muscle cells (SMCs) and SMC-derived extracellular matrix (Lusis, 2000). Carotid plaques are clinically defined as the presence of focal wall thickening that is at least 50% greater than the surrounding vessel wall or as a focal region with a carotid intima media

thickness (IMT) greater than 1.5 mm that protrudes into the lumen, distinct from the neighboring vessel (Stein, et al., 2008). Cytokines and growth factors secreted by macrophages and T cells assist in SMC migration and proliferation as well as extracellular matrix production. Inflammatory cytokines, matrix-degrading proteases and adhesion molecules are produced after CD40, expressed on macrophages, endothelial cells and SMCs, interacts with its ligand, CD40L. Various risk factors increase the development of fibrous lesions, including elevated homocycteine, hypertension and hormones. For example, elevated levels of homocycteine and angiotensin II (increases blood volume and blood pressure) stimulate the migration or proliferation of SMCs (Lusis, 2000). Intimal SMCs secrete extracellular matrix and brings about a fibrous cap over the forming plaque. Fibrous plaques are the fourth stage of atherosclerosis.

Complex Lesions and Thrombus

Complex lesions and thrombosis depicted in Figure 2 is the final and most severe stage of atherosclerosis. Studies suggest that the development of thrombus-mediated acute coronary events depend more on the composition and vulnerability of plaque than the severity of stenosis (Lusis, 2000). Thin fibrous caps and increased inflammatory cells cause a plaque to be more vulnerable. Thin fibrous caps result when matrix is degraded by proteinases like collagenases, gelatinases, stromolysin and cathepsins and when matrix secretion is inhibited. When plaque is vulnerable, an event like infection can destabilize it causing it to rupture and leak its contents on the innermost side of the intima, sometimes obstructing the lumen. As a result, a thrombus is formed. A thrombus is a blood clot that remains at the site of formation in a blood vessel. Calcification and neovascularization are common in advanced lesions and also jeopardize the stability of atherosclerotic lesions. Plaque rupture often happens at the edges of a lesion where foam cells are abundant. This suggests that inflammation may promote thrombosis. A thrombus consists of adherent platelets and fibrin crosslinks. Any loose, broken

off material flows in the blood stream until wedged inside the lumen of a smaller vessel and blood flow is restricted.

The American Heart Association defines atherosclerotic stages similar to above except complex lesions is a stage of its own and a sixth stage describes one of three disruptions of the lesion surface: surface defects, hematoma and thrombosis (Herbert C. Stary; A. Bleakley Chandler; Robert E. Dinsmore; Valentin Fuster; Seymour Glagov; William Insull, 1995). Structural defects include fissures and ulcerations influenced by inflammatory cells, coronary spasms, structural weakness, shear stress and macrophage foam cells. Fissures often reseal incorporating hematomas and thrombi into the lesion. Hematomas in the intima are typically caused from tears in the lumen surface but may result from hemorrhages in newly formed blood vessels. Thrombi are blood clots resulting from lesions and are favored in individuals with high plasma fibrinogen (Herbert C. Stary; A. Bleakley Chandler; Robert E. Dinsmore; Valentin Fuster; Seymour Glagov; William Insull, 1995).

Regardless of the atherosclerotic stage definition, complex lesions and thrombus can result in a narrowing in the arterial lumen, further destruction of the intima and media and detached thrombotic debris in the blood stream.

Ultrasound Measure of Intima Media Thickness

An ultrasound machine transmits high frequency sound waves through a probe into the area of the body the probe is held next to. The sound waves hit a barrier and reflect back to the probe where an image of the barriers is created based on the elapsed time between the transmission and receiving of the sound wave. While some sound waves reflect back others will continue further into tissue and reflect back off of deeper barriers. A barrier is an area of transition, for example, from fluid to soft tissue or soft tissue to bone. Ultrasound picks up the barrier between the lumen of an artery and the tunica-intima and the barrier between the tunica-media and the tunica-adventitia. However, since the tunica-intima and tunica-media are similar tissues the ultrasound cannot differentiate between the two

layers. As a result, the tunica-intima and tunica-media are measured together as one thickness, even though lesions mostly affect the tunica-intima layer (Anjan K. Sinha, 2002). Any thrombus development or growth on the intima or endothelial cells is also measured as part of this thickness. The width of the tunica-intima and media and any associated buildup is termed the intima-media thickness (IMT).

The IMT enlarges, or thickens with increased atherosclerosis. This is due to the buildup of lipoproteins, inflammatory cells (including foam cells) and migrating SMCs in the intima. Thrombus development also increases IMT. Furthermore, ultrasound imaging provides information on not only IMT but plaque presence and type, calcification and wall diameter (Anjan K. Sinha, 2002) so great insight on a person's atherosclerotic development can be gained through ultrasound of an artery. Atherosclerotic disease is a major factor in the intima-media growth.

Carotid artery IMT is often used as a surrogate marker for atherosclerotic disease and a way to detect subclinical atherosclerosis (Cobble & Bale, 2010). Since carotid artery IMT is a marker of atherosclerosis and atherosclerosis is a well-known component of CVD, carotid artery IMT can help evaluate CVD risk allowing for additional preventative measures or early treatment of the disease. Carotid artery IMT is non-invasive, relatively inexpensive, a reproducible technique and capable of being repeatedly performed without adverse effects (Cobble & Bale, 2010; Stein, et al., 2008). Many studies have validated carotid artery IMT and plaque as an accurate marker of atherosclerosis.

CVD can be identified using carotid artery IMT. Gepner et al. recorded the CVD risk measurements, carotid artery IMT and vascular age of 506 people. They reported that carotid artery IMT accurately measured CVD and identified advanced subclinical atherosclerosis. Identifying pre-symptomatic atherosclerosis significantly changed individuals CVD risk profile (Hooker, et al., 2005). In another study, Chambless et al. observed 7,289 pre-symptomatic women and 5,552 pre-symptomatic men aged 45-64 years over 4 to 7 years and found carotid artery IMT predicted future CHD. Also, women were found to be less likely of developing CHD at a less severe IMT compared to men. After a

1mm mean carotid artery IMT women had similar likelihood as men of developing CHD.   IMT correctly

forecasts an individual's probability of developing CVD.

IMT is an accurate predictor of future cardiovascular events. O'Leary, et al. found that increases

in carotid artery IMT, measured with ultrasound, is directly associated with increased risk of MI and

stroke in older adults without a history of CVD (O'Leary, et al., 1999). After measuring the carotid artery

IMT in 5858 men and women, the relative risk of the highest quartile group having an MI or stroke was

3.87 times that of the lowest quartile. In a meta-analysis Lorenz, et al. found carotid artery IMT to be a

strong predictor of future vascular events, defined as MI, angina pectoris, coronary intervention, stroke

or transient ischemic attack (TIA) (Lorenz, et al., 2007). Common cardiovascular incidents like an MI or

stroke can be foreshadowed based on IMT.

Plaque is also a way of evaluating a person's CVD risk. Wyman et al. (2006) observed carotid

plaque to be associated with both traditional (age, tobacco use, total cholesterol, systolic blood pressure

(SBP), family history, angina, diabetes mellitus, total body mass index, weight, etc.) and non-traditional

cardiovascular (stress, genetic disposition, degree of ST segment depression, etc.) risk factors. Schmidt

et al. showed that men with non-stenotic plaques in the femoral artery and no previous history of

cardiovascular events had an increased chance of having future cardiovascular events (Schmidt, et al.,

2005). Another method for projecting CVD risk, similar to IMT is plaque development.

Carotid Ultrasound Technique

Carotid ultrasound should always be performed by a trained researcher using up to date

equipment or else images won't correctly reflect carotid artery IMT. There is no standardized protocol

for measuring the carotid artery IMT, however, the Society of Atherosclerosis Imaging and Prevention

(SAIP) is currently drafting a protocol (Cobble & Bale, 2010).

Images are typically recorded in at least one of three parts of the carotid artery (seen in Figure

3): the common carotid, the carotid bulb and the internal carotid artery. A complete image will show

both a near and far wall of the carotid artery. The two boarders, lumen to intima and media to

adventitia, are seen in Figure 4 and traced using a tracing tool. The thickness is measured electronically.

In addition, a transverse view of the carotid artery can further reveal plaques (Cobble & Bale, 2010).

Carotid ultrasound can be done using B- and M-mode sonography. "B" stands for brightness as

the brighter an image is the stronger the echo feedback is. M-mode sonography records motion coming

towards and away from the transducer. B-mode is most common and practiced with carotid ultrasound

(Anjan K. Sinha, 2002).

Since atherosclerosis is not uniform throughout a vessel, it's suggested that a summary of

indices of IMT is used (Anjan K. Sinha, 2002).   Commonly, the far wall of the carotid artery is measured

as the clarity of the near wall depends on gain settings and can be inaccurate (P.J Touboul, 2004). It's

suggested that carotid artery IMT be measured over a 10 mm segment of the carotid artery that is 1 cm

proximal to the common carotid bifurcation (P.J Touboul, 2004). From each segment the average IMT is

measured and recorded from the saved image.   Significant plaques are generally excluded from the IMT

measurement but can be measured and included in a detailed report.

Carotid plaque is an independent risk factor for CVD (Cobble & Bale, 2010; Sutton-Tyrrell, 1998).

Total plaque burden can be measured by adding up all the plaques identified bilaterally (Cobble & Bale,

2010). There are different types of plaque that can be recognized by a trained sonographer; however

this differentiation is subject to human error. Types of plaque include soft, heterogenous mixed and

fully calcified. Understanding plaque type and amount helps clarify CVD severity.

Interpretation of Carotid Artery IMT

There are no standardized guidelines defining low, moderate or high risk IMT, only reference

values. Cobble et al. describes reference values for both carotid artery IMT and plaque.

A moderately high risk is a carotid artery IMT <1 mm and in the 50th-75th percentile for their age,

sex and race. They have no plaques.

A high risk of CVD will have a carotid artery IMT ≥1 mm or be greater than the 75th percentile. Or, they will have less than a 50% plaque stenosis, independent of carotid artery IMT requirements.

A very high risk person will have a carotid artery IMT ≥1 mm or be greater than the 75th percentile. Or, they will have greater than or equal to 50% plaque stenosis, independent of carotid artery IMT requirements.

These guidelines can help categorize a person's risk based on ultrasound carotid artery IMT and plaque findings. SAIP's anticipated guidelines will provide additional threshold values and the risks associated with them.

Demographics

Different populations may be more or less likely to have atherosclerosis and larger carotid artery IMT. Researchers have reported differences between gender, age and socioeconomic groups.

There appears to be a significant trend between gender and IMT. Kablak-Wiembicka et al. reported that those with coronary artery disease (CAD) had larger IMT values than those without CAD, regardless of gender. Of those without CAD, women had lower mean IMT values compared to men. Women also had significantly lower IMT thresholds for likelihood of CAD; a mean IMT of 1.069 mm in women was highly predictive of developing CAD compared to 1.153 mm for men (Kablak-Ziembicka, et al., 2005). Lawlor et al. explored weight distribution as a possible explanation for gender differences in IMT. After adjusting for waist-to-hip ratio (WHR), sex differences in carotid artery IMT were removed, (Ainsworth, 2002) thus, a possible explanation for women having a lower IMT compared to men is their distribution of body fat (WHR) compared to men.

Atherosclerosis starts at a young age and accelerates with old age. Vascular changes are associated with obesity even in children. Obese boys and girls aged 9 to 13 years had an increased IMT compared to non-obese boys and girls (Reinehr, Kiess, de Sousa, Stoffel-Wagner, & Wunsch, 2006). These elevated IMT results were consistent with concurrent CVD risk factors of hypertension, chronic

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inflammation and impaired glucose metabolism. Davis et al. studied how risk factors during childhood influenced IMT later in life (P. H. Davis, Dawson, Riley, & Lauer, 2001). Childhood risk factors of total cholesterol in both boys and girls and body mass index (BMI) in girls predicted adult carotid artery IMT. LDL cholesterol in both sexes and diastolic blood pressure (DBP) in women independently predicted carotid artery IMT. Risk factors measured as early as 8 to 11 years of age predicted carotid artery IMT in adults up to 42 years. CVD can manifest itself in young populations influencing IMT in later years.

In a population without CVD, women appear to have smaller carotid artery IMT compared to men. After menopause, however, both men and women have comparable carotid artery IMT. Carotid artery IMT increases with age but slower in women than in men. After women reach 65 years of age, however, carotid artery IMT differences disappear (Kablak-Ziembicka, et al., 2005). In looking at pre and post-menopausal women, Sutton Tyrrell et al. reported an increase in mean IMT and plaque after, compared to before, menopause (P.J Touboul, 2004). Mean IMT was 0.69 mm among premenopausal women and 0.77 mm post-menopause (P<0.001). Prevalence of plaque was 25% before menopause and 54% after (P<0.001). Risk factors of pulse pressure (P<0.001), triglycerides (P=0.002), BMI (P<0.001) and study group (divided by both age and menopausal status) (P<0.001) were all significantly higher 5-8 years post-menopause. While healthy women have smaller IMT than men during their premenopausal years it appears that changes during menopause equalize IMT between genders.

Deans et al. examined the IMT and plaque development between different socioeconomic groups in the NHS Greater Glasgow Health Board area. Carotid IMT and plaque were significantly worse in participants from the bottom 5% of areas classed by the Scottish Index of Multiple Deprivation than participants in the top 20% (Deans, et al., 2009). Differences in plaque scores were more statistically significant and appeared at an earlier age than IMT. Inflammatory markers were significantly higher in deprived groups compared to more privileged groups. This study indicates that less affluent areas may

have a greater population percentage with higher IMT and plaque scores compared to more affluent

areas.

Exercise and IMT

It is common knowledge that increased physical activity is associated with decreased blood

pressure, diabetes, LDL cholesterol and many other risk factors of CVD. Theoretically, higher levels of

physical activity should also decrease atherosclerosis and carotid artery IMT. Research, for the most

part, agrees with this correlation.

Aerobic exercise increases blood HDL levels. In a randomized controlled trial experiment,

aerobic exercise was the primary intervention in women over 18 years of age between 1955 and 2003.

Women in the treatment, exercise group had increased HDL levels and decreased total cholesterol, LDL

and triglycerides by 2%, 3% and 5%, respectively, compared to the sedentary, control group (Eapen,

2009; Kelley, 2005). While LDL cholesterol increases IMT, HDL helps remove excess cholesterol from

peripheral tissues and inhibits lipoprotein oxidation (Lusis, 2000).

Two studies have reported the influence of exercise on carotid artery IMT in pre- and post-

menopausal women.   Wildman et al. wanted to learn if progression of carotid atherosclerosis observed

in middle-aged women was related to menopause or lifestyle intervention. A group of women had

three carotid artery IMT measurements over a 7.5 year period. Findings showed that accelerated

subclinical atherosclerosis was associated with the menopause transition and that diet/exercise

interventions slowed atherosclerotic progression (Wildman, et al., 2004). Moreau et al. studied the

effects of hormone replacement therapy (HRT) and habitual endurance exercise on femoral and carotid

artery IMT in healthy postmenopausal women. There was an endurance trained and sedentary group

and women in each group received either HRT or no HRT. Data showed that both endurance training

and HRT independently were associated with a smaller IMT (Moreau, et al., 2002). Increased physical

activity is related to a decrease IMT in postmenopausal women.

A cross-sectional survey done in northeast Germany evaluated the relationships between physical activity, dietary patterns, and cardiovascular risk factors (Luedemann, et al., 2002). Carotid artery IMT and other information were collected from 1632 individuals between the ages of 45 and 70 years of age. Participants were categorized into an optimal lifestyle group or unfavorable lifestyle group. In people who had never smoked there was a significant decreasing trend between IMT and severe asymptomatic atherosclerosis from unfavorable to optimal lifestyle groups. This trend was not consistent with smokers. There was increased risk of severe asymptomatic atherosclerosis in participants of the unfavorable group compared to participants with an optimal lifestyle. This indicates that an optimal lifestyle characterized by a healthier diet and increased physical activity decreases IMT.

Sedentary behavior and vigorous physical activity was studied in a healthy, middle aged (mean age = 44±8 years) population of men and women (Kozakova, et al.). Physical activity was measured using an accelerometer (mean monitoring time = 5.7±1.5 days) and time spent in sedentary, light, moderate and vigorous activities was determined. Common carotid IMT was measured at baseline: before wearing the accelerometer, and three years later. After three years IMT was significantly lower in subjects with periods of vigorous activity compared to subjects with only light activity or periods of moderate activity.

Physical activity's relation to carotid artery IMT was also studied in a population of patients with CHD (Sato, et al., 2008). After receiving an exercise prescription participants walked for 6 months and carotid artery IMT was reported 6 times each month. Results suggested that carotid artery IMT progression could be slowed in CHD patients who increased their daily walking. Patients who walked more than 4.25 km a day had significantly reduced carotid artery IMT progression. For secondary prevention of CVD a walking distance of 4-5 km each day is recommended.

Carotid artery IMT was correlated to endurance exercise, recreational exercise and a sedentary lifestyle in men and women 20 to 40 years of age (Popovic, et al.). An endurance athlete was classified

as anyone performing ≥3 hours of running and/or cycling and/or swimming per week consistently for at least 6 months. A recreational athlete was defined as anyone performing ≥3 hours of general sports per week. These sports could include endurance activities as long as endurance activities were done less than 3 hours a week. Both recreational and endurance exercise was correlated to a preventative influence against cardiovascular risk; risk factors were reduced. However, carotid artery IMT was not significantly different in athletic groups compared to the sedentary group.

Not all articles have agreed that exercise has a beneficial effect on IMT. A study looking at regular aerobic exercise and age-related increase in IMT in healthy men proved the null (Tanaka, et al., 2002). There was both a cross-sectional and interventional part to the study. Cross-sectionally, 137 sedentary or endurance trained men had their carotid artery IMT measured. There were no significant differences between IMT and endurance trained men at any age. For the second part of the study 18 healthy men were measured before and after 3 months of endurance training. The exercise intervention consisted of an initial low-intensity exercise of 25-30 min/day, 3-4 days/wk (about 60% HRmax). After increasing exercise tolerance, walking increased to 40-45 min/day, 4-6 days/wk working at 70-75% HRmax. Carotid artery IMT, IMT/lumen ratio, and SBP did not change with 3 months of exercise training. Tanaka et al. found endurance exercise ineffective at reducing IMT.

In summary, physical activity appears to be associated with decreased IMT. Research was done in menopausal populations; a representative German population; healthy, young-to-middle age populations; and a CHD population. Overall, it appears that physical activity is correlated to decreased carotid artery IMT.

Despite what is known on physical activity and carotid artery IMT, little is known on sports participation and its correlation with carotid artery IMT. One study looked at recreational activity in young adults but recreational activity was defined broadly as playing sports and not individual, specified sports (Popovic, et al.). There are a range of sports, each requiring different intensities and duration of

play. Different sports have different energy requirements. To assist in studying these varying energy requirements, a sport can be assigned a metabolic equivalent (MET) value. Assigning sports to their associated MET value allows for sports to be organized in order of increasing energy requirement. Using a regression analysis to find the correlation between MET values and carotid artery IMT is an effective way to learn what MET values tend to be associated with lower carotid artery IMT.

The annual Huntsman World Senior Games (HWSG) is an excellent event promoting physical activity in older populations. Seniors must be 50 years of age to compete and 26 sports are available for competition. The HWSG are an ideal place to study the relationship between sports participation and carotid artery IMT.

Chapter 3

METHODS

Participants

Participants will include between 200 to 400 men and women who are at least 50 years of age,

competing in the 2010 annual Huntsman World Senior Games (HWSG). Participants will be recruited by

placing announcements advertising an opportunity to participate in a cardiovascular risk study in each

participant registration packet. Participants will also be recruited from those attending the Health Fair

that is provided for all participating athletes. Thus, participants will be recruited from all 26 venues. In

addition, announcements will be distributed at select venues to recruit participants from events that

require minimal energy expenditure (e.g., bridge, archery, chess) and events that require higher levels of

energy expenditure (e.g., cycling, track and field, swimming, road races, triathlon).

All data collection will occur after this study has been reviewed and approved by the Brigham

Young University Institutional Review Board (IRB). Participants will voluntarily participate in this study.

All study participants will read and sign an informed consent form prior to their participation.

Design

This is an observational cross-sectional study.

Procedures

All data collection will be conducted during the 2 weeks of the 2010 HWSG in St. George, Utah.

Specifically, data collection will occur during the Health Fair which is held for three days, each of the two

weeks of the HWSG.

The first of each three day period of data collection will be dedicated as a service-oriented

health screening that is open to all HWSG participants and their spouses or other guests. Participants

for data collection will be recruited as described above and will participate in the data collection by

appointment. The second and third day of each week of health fair will be dedicated for data collection.

All data collection will be conducted during a single visit. Results of all measurements will be mailed (or emailed) to participants several weeks following the HWSG.

Data Collection

Data collection includes completion of a brief health history and a sports participation survey (Appendix A) and the measurement of height, weight, waist and hip circumferences, body composition, resting blood pressure, and carotid artery IMT. From this data, body mass index (BMI; kg/m^2), waist-to-hip (WHR) ratio, pulse pressure and mean arterial pressure will be calculated.

METS

Each sport will be given a corresponding MET value to standardize the energy requirement of sports. A MET is the metabolic equivalent of an activity compared to rest, or how much more energy an activity requires compared to at rest. The assigned MET value will be taken from The Compendium of Physical Activities Tracking Guide (Ainsworth, 2002). The highest MET value will be recorded and used for analysis if study participants are competing in more than one event.

Height and Weight (BMI)

Each participant's height (inches and centimeters) will be measured and recorded using a calibrated wall scale measured to the nearest one-quarter inch. Weight will be measured to the nearest tenth of a pound, recorded and converted to kilograms for each participant using a digital scale (Healthometer Professional, Model 349KLX/320KL, Sunbeam Products, inc., BOCA RATION, FL 33431, USA).

Waist/Hip Circumference

Waist and hip circumferences will be measured as described by ACSM to the nearest half inch and half centimeter while in the standing position using a spring-loaded Gulick tape measure (Walter R. Thompson, 2010). Waist circumference will be measured at the narrowest circumference between the umbilicus and the xyphoid process. If there is not a narrowing of the waist within this area, the waist

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circumference will be measured at the level of the umbilicus. The hip circumference will be measured at

the widest part of the buttocks with both feet together. Each circumference will be measured three

times. If two of the measurements are the same that number will be recorded. If all three

measurements are different, then an average of all three measurements will be calculated and

recorded. If a measurement differs more than half an inch from the other two measurements then the

circumference will be re-measured. A waist-to-hip ratio will be calculated by dividing the recorded waist

circumference by the recorded hip circumference.

Resting Blood Pressure

Resting blood pressure will be measured in the left arm using an automated blood pressure

monitor (Omron Model HEM-780, Omron Healthcare, Inc., Bannockburn, Illinois, USA). Three

consecutive blood pressure measurements will be made in the seated position after at least 5 minutes

of rest. The average systolic and diastolic blood pressure will be recorded.

Body Fat

Body fat percentage will be measured using a hand held bioelectrical impedance device (Omron

Model HBF305 Omron Healthcare, Inc., Bannockbum, Illinois, USA). This device has been found to be a

valid estimation of body fat percentage (Bertoli, Petroni, Spadafranca, Dorigo, & Testolin, 2003). A

volunteer research assistant will assist each participant in using the device. Age, gender, height, and

body weight will be entered into the device. Participants will then hold the device in the standing

position with both arms extended in front of their body. Percent body fat will be recorded from the

displayed value. Measurements will be recorded to the nearest tenth of a percent.

High-Resolution Carotid Ultrasound

This study will use the methodology described and validated by Fritz (Hajri, et al., 2007) for the

SonoCalc automated software analysis ultrasound system. Ultrasound images will be taken from the

right and left common carotid artery using a Sonosite Titan Ultrasound system (Sonosite Inc., Bothell,

WA,USA), a B-mode, high-resolution ultrasonograph. A 5-MHz traducer will be used to take images from an anterior, medial and posterior view. Different views allow images of the arterial wall to be captured at different angles. IMT will only be measured in the far wall of the artery as the IMT values of the near wall are less reliable (P.J Touboul, 2004). A minimum of 10 mm of common carotid artery will be captured in an image. All images will be taken 1 cm proximal to the common carotid bifurcation. While two technicians will be measuring carotid artery IMT concurrently, one technician will capture all 6 views of the common carotid arteries for an individual.

Manual analysis of the common carotid artery will be done according to Fritz's (Hajri, et al., 2007) outline when the specified segment is unclear and the software cannot identify the intima/lumen surface. Images will be analyzed by a trained and experienced investigator using the SonoCalc software system. Average IMT values for the right and left common carotid arteries and the average IMT value for all six measurements (right and left common carotid combined) for each participant will be recorded and used for data analysis.

Blood Tests

Participants will be asked to fast 8-12 hours before having their blood drawn. One and one-half teaspoons (7.5 mL) of blood will be drawn during scheduled appointments and walk-in visits by trained phlebotomists. Assays will include a lipid panel, fasting blood glucose (FBG), high sensitivity C-reactive protein (hs-CRP) and hemoglobin A1C test (HbA1C). The lipid panel will include blood triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), very low-density lipoprotein cholesterol (VLDL-C) and total cholesterol (TC). All blood samples will be chilled in ice until analyzed locally in St. George by LabCorp.

Statistical Analysis

Regression analysis will be done to determine the relationship between the energy expenditure of the 26 sporting events held at the 2010 Huntsman World Senior Games and carotid artery IMT.

Covariate factors anticipated in this study are number of years participation in sport of choice, gender, age, WHR, height, weight, BMI, percent body fat, blood pressure, TC, HDL-C, LDL-C, VLDL-C, TG, FBG, hs-CRP, HbA1C and factors gathered from participants health history.

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List of Figures

Figure 1. Anatomy of a normal large artery. (Lusis, 2000)
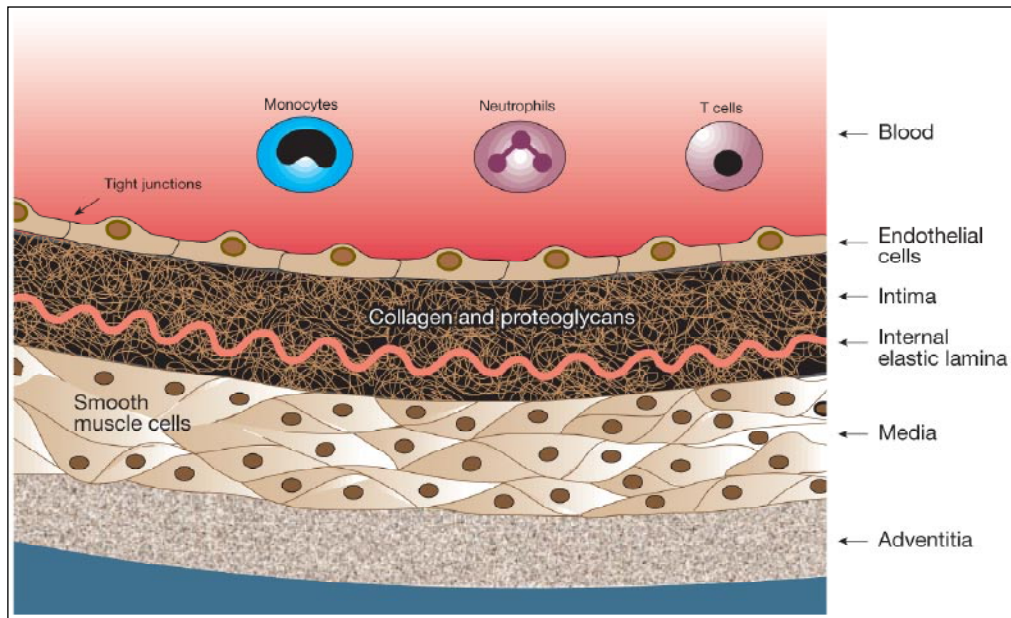
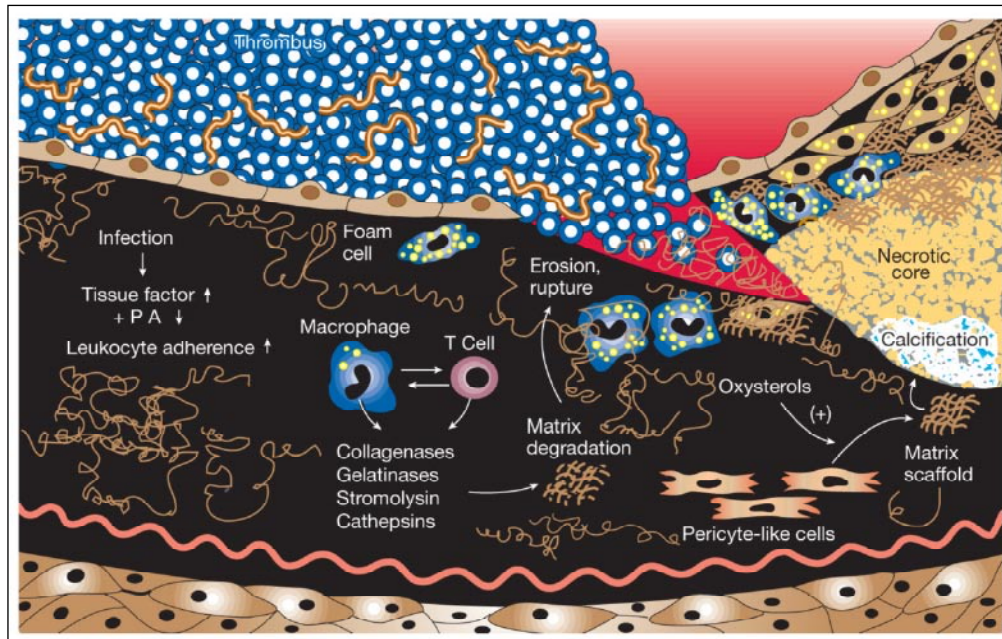Figure 2. Complex lesion and thrombus. (Lusis, 2000)

Figure 3. The three sections of the carotid artery commonly measured using ultrasound:

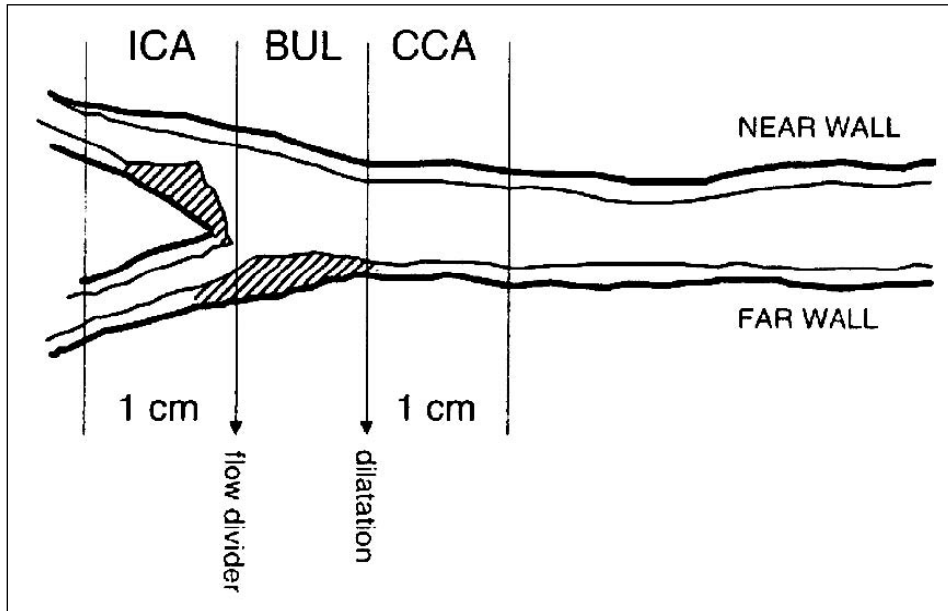common carotid, carotid bulb and internal carotid artery. (Anjan K. Sinha, 2002)
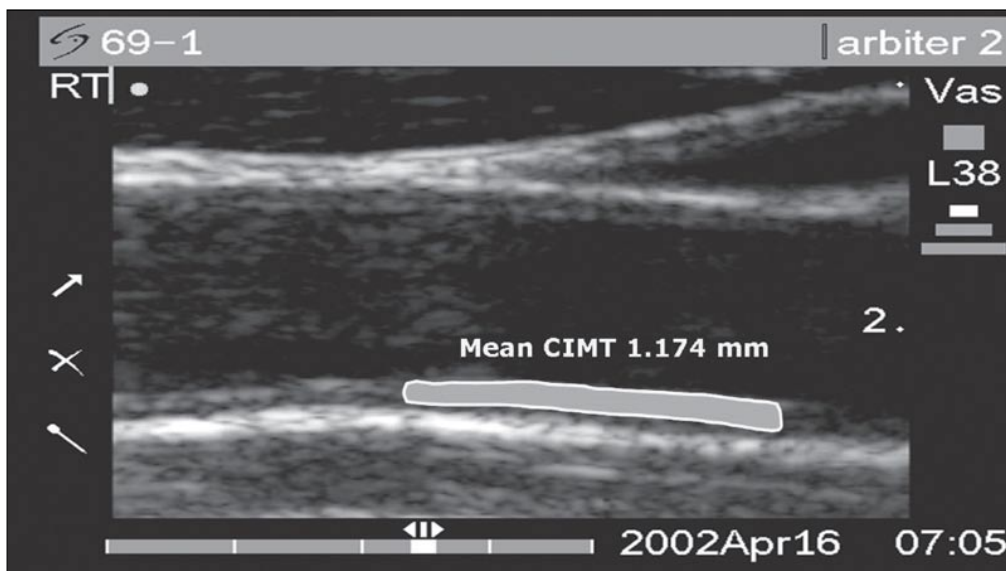
Figure 4. The near and far boarders of a carotid artery representing the lumen side of the

intima and the adventitia side of the media. (Cobble & Bale, 2010)

Appendix

Consent to be a Research Subject

Introduction. Ultrasound can be used as a screening tool to identify the early stages of atherosclerosis in the carotid arteries and help clarify the risk of cardiovascular disease. The purpose of this study is to clarify the influence of a various cardiovascular risk factors on the thickness of the wall of the carotid arteries in men and women across the age span and in different cultures. You have been invited to participate in this study because you are at least 18 years of age. This research study is being conducted by Pat Vehrs, Ph.D. and Ron Hager, Ph.D., faculty in the Department of Exercise Sciences at Brigham Young University, in Provo, Utah.

Procedures. You will be asked to consent to the following measurements and procedures:
Complete a short questionnaire regarding cardiovascular risk factors, symptoms of cardiovascular disease, and your current health status. This will take less than 5 minutes.
Have the following measurements taken: height, weight, waist and hip circumference, resting blood pressure, and body composition. This will take less than 15 minutes.
After fasting for about 8 hours, have about 1-2 tablespoons of blood drawn from your arm either at the same time other measurements are taken, or at a nearby clinic or hospital (you will be given instructions on where to go).
Participate in an ultrasound carotid artery screening. This will take less than 20 minutes.

All procedures will be conducted by the principal investigators or other trained personnel. The body composition assessment will be done using a handheld electrical impedance device. Height, weight, and hip and waist circumferences will be measured while wearing minimal clothing (no shoes, jackets, etc.). Blood pressure will be measured on your arm using an automated device. You will rest lying down in a face-up position for about 10 minutes before digital images are taken of the carotid arteries in your neck using an ultrasound device. A gel will be applied to your neck before taking the images. Three images will be taken of the carotid artery on each side of your neck. The images will be saved to a computer for analysis. Not including the time it takes to have blood drawn, your total time commitment is expected to be less than one hour.

Risks/Discomforts. There are minimal risks for participation in this study. However, you may feel some discomfort when answering questions about personal health history or when height, weight, waist and hip circumference, body composition, and blood pressure measurements are being taken. You may also feel some discomfort or anxiety while participating in the carotid artery ultrasound screening, however this screening and the other measurements are non-invasive. Any foreseeable risks, such as bruising or infection, associated with drawing blood will be minimized by having your blood drawn by a nurse or phlebotomist on-site or at a local clinic or hospital.

Benefits. You will be given information about all of the measurements taken, blood tests results, measurements taken of your carotid arteries, and an explanation of the results. The carotid artery ultrasound screening will not be used to diagnose cardiovascular disease.

_____ initials

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Confidentiality. The information that will be kept by the principal investigator includes your name; contact information; responses to the health questionnaire; carotid artery and all other measurements.

We will be keeping your name and contact information so we can contact you about your results. Your results will be made available to you in any one of a variety of ways, including reviewing them at the time the measurements are taken, receiving them by mail or email, or by accessing a web-based information center.

With your permission, we may also contact you over the next few years to invite you to participate in a follow-up study similar to this again or to complete on-line surveys about topics relating to cardiovascular risk. When contacted, you can choose to participate in the study or not. Your contact information will be shared with members of the research team as needed only to send you information about participating in another study. If you do not wish to be contacted in the future, your contact information will only be used as needed to give you the results of this study.

All information provided will remain confidential and will only be reported as group data without reference to any identifying information. All of your information and measurements will be kept in a secured office and computer. Only those directly involved with the research will have access to the data.

Compensation. You will not receive any type of compensation for participating in this study.

Participation. Your participation in this research study is entirely voluntary. You have the right to withdraw at anytime or refuse to participate entirely.

Questions about the Research. If you have questions regarding this study, you may contact Pat Vehrs Ph.D. at 801-422-1626, by email at pat_vehrs@byu.edu or in person in 116B Richards Building. You may also contact Ron Hager, Ph.D. at 801-422-1183, by email at hager@byu.edu or in person at 228B Smith Field House.

Questions about your Rights as Research Participant. If you have questions regarding your rights as a research participant, you may contact the IRB Administrator in person in A-285 ASB at Brigham Young University, Provo, UT; by phone at 801-422-1461; or by email at irb@byu.edu.

I have read, understood, and received a copy of this consent form and desire of my own free will to participate in this study.

_____   _____   _____
Name (printed)   Signature   Date

☐   I do not want to be contacted by Drs. Vehrs or Hager about future research in topics relating to cardiovascular risk.

Questionnaire
Instructions: Please complete all information on the front and back side of this page.

_____   _____   Date of Birth   _____ / _____ / _____

First Name   Last Name   month / day / year

_____   _____   ____ _____

U.S. Mailing Address   City   ST   Zip

_____

Mailing Address if you live outside of the U.S.

_____

Email Address

_____   ☐ Male ☐ Female

Age

☐ Caucasian   ☐ African American   ☐ Hispanic / Latino   ☐ American Asian

☐ Pacific Islander   ☐ American Indian   ☐ Other _____

How many years have you been competing in the Senior Games in your state or in the World Senior Games? _____

Which sports are you participating in <u>this year</u> (check all that apply)?

How long have you trained for competition in this sport?

☐	Archery_____		☐	Pickleball_____	
☐	Badminton_____		☐	Racquetball_____	
☐	Basketball_____		☐	Shooting_____	
☐	Bowling_____		☐	Soccer_____	
☐	Bridge_____		☐	Softball_____	
☐	Chess_____		☐	Square Dancing_____	
☐	Cowboy Action Shooting_____		☐	Table Tennis_____	
☐	Golf_____		☐	Tennis_____	
☐	Horseshoes_____		☐	Volleyball_____	
☐	Lawn Bowls_____		☐	Volleyball – Global Cup_____	

☐ Cycling   ☐ Hill Climb   ☐ Time Trial   ☐ Criterium   ☐ Road Race

☐ Mountain Biking   ☐ Hill Climb/Down Hill   ☐ Cross Country

☐ Racewalk   ☐ 1500   ☐ 3000   ☐ 5000

☐ Road Race   ☐ 5K   ☐ 10K   ☐ ½ Marathon   ☐ Triathlon

☐ Swimming   ☐ 50   ☐ 100   ☐ 200   ☐ 400   ☐ 800   ☐ 1500   ☐ Relays

☐ Track and Field   ☐ 50   ☐ 100   ☐ 200   ☐ 400   ☐ 800   ☐ 1500   ☐ 3000   ☐ Relays   ☐ Jumps/Throws

Answer each question by checking either the **YES** or **NO** box. If you are uncertain, skip the question.

Yes	No	
☐	☐	Do you have a father or brother who had a heart attack or heart surgery before the age of 55 or a mother or sister who had a heart attack or heart surgery before the age of 65?
☐	☐	Do you smoke now or have you quit smoking in the last 6 months?
☐	☐	Do you get less than 30 minutes of moderate-intensity physical activity during three or more days per week?
☐	☐	Do you take medications to control your blood pressure?
☐	☐	Has your doctor ever told you that you have a heart condition?
☐	☐	Do you have chest pain during physical activity or exercise?
☐	☐	Do you have chest pain at rest or doing usual activities?
☐	☐	Do you experience unusual shortness of breath when resting or with usual activities?
☐	☐	Do you have shortness of breath during physical activity or exercise?
☐	☐	Do you have difficulty breathing when reclined, lying down or sleeping?
☐	☐	Do you experience dizziness, fainting, or blackouts?
☐	☐	Do you have swelling of the ankles?
☐	☐	Do you have (or have you had) sensations of a rapid or irregular heart beat?
☐	☐	Do you have burning or cramping sensations in your legs when walking?
☐	☐	Do you lose consciousness or balance because of dizziness?

Do you have any of the following (check all that apply)?

- ☐ Cardiovascular disease
- ☐ Coronary heart disease
- ☐ Diabetes
- ☐ Heart murmur
- ☐ Heart valve disease
- ☐ Kidney disease
- ☐ Liver disease
- ☐ Pacemaker
- ☐ Pulmonary disease such as asthma, cystic fibrosis, interstitial lung disease, or COPD
- ☐ Stent

Have you ever had any of the following (check all that apply)?

- ☐ Heart attack
- ☐ Stroke
- ☐ Any kind of heart surgery, including catherization, angioplasty, bypass, or valve replacement

Are you currently taking any prescription medications?

- ☐ No
- ☐ Yes   For what? _____

    _____

☐ Blood Draw Completed
☐ Permission to Contract

_____ _____
Name   ID

Height   _____ in   Weight: _____ pds

Waist Circumference   _____ in   Hip Circumference _____ in

Body Fat   _____ %

Resting Blood Pressure: _____ / _____

Right Carotid Artery Anterior View _____

          Direct View _____

          Posterior View _____   Average Right IMT _____

Left Carotid Artery Anterior View _____

          Direct View _____

          Posterior View _____   Average Left IMT _____

                          Combined Avg IMT _____

2010 Huntsman World Senior Games			
Sport	Event	MET Value	MET group
Bridge		1.5	Low Exercise Intensity
Chess		1.5	
Cowboy Action Shot		2.5	
Shooting		2.5	
Bowling		3	Moderate Exercise Intensity
Horseshoes		3	
Archery		3.5	
Lawn Bowls		4	
Table Tennis		4	
Track and Field	Shot Put, discus	4	
Golf		4.5	
Square Dancing		4.5	
Softball		5	
Pickleball		5	
Tennis	Doubles	6	Vigorous Exercise Intensity
Tennis	Mixed Doubles	6	
Track and Field	Jumps, Javelin	6	
Racewalk		6.5	
Badminton		7	
Swimming	Backstroke	7	
Swimming	Freestyle- slow, moderate	7	
Tennis	Social Round Robin	7	
Racquetball		7	
Basketball		8	
Tennis	Singles	8	
Track and Field	5mph, 12min/mile	8	
Mountain Biking		8.5	
Road Race	cross country	9	
Track and Field	5.2mph, 11.5min/mile	9	
Track and Field	cross country	9	
Cycling	14-15.9 mph, racing or leisure, fast, vigorous effort	10	
Soccer		10	
Swimming	Breaststroke	10	
Swimming	Freestyle-fast vigorous	10	
Track and Field	6mph, 10min/mile	10	

Track and Field	running on a track, team practice	10	
Swimming	Butterfly	11	
Track and Field	6.7mph, 9min/mile	11	
Track and Field	7mph, 8.5min/mile	11.5	
Cycling	16-19mph,racing/not drafting or >19mph,very fast,racing	12	
Track and Field	7.5mph, 8min/mile	12.5	
Track and Field	8mph, 7.5min/mile	13.5	
Track and Field	8.6mph, 7min/mile	14	
Track and Field	9mph, 6.5min/mile	15	
Track and Field	10mph, 6 min/mile	16	
Track and Field	10.9mph, 5.5 min/mile	18	
Triathlon		9 to 16	