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Comparison of carotid, brachial, and popliteal intima media thickness among sedentary and physically active subjects between 40 and 60 years old

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Comparison of Carotid, Brachial, and Popliteal Intima Media Thickness

Among Sedentary and Physically Active Subjects

Between 40 and 60 Years Old

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Abstract

The purpose of the current study was to determine the effect of long term versus recent training on intima-media thickness (IMT) and if this effect is localized in the vascular beds of the tissues directly involved in the activity. Thirty-four male subjects (aged 49.69 ± 6.48 years) were recruited and divided into the following groups: sedentary (SE), recent aerobic exercisers (RE) or long-term aerobic exercisers (LE). Carotid, brachial, and popliteal artery IMT was measured using B-mode ultrasonography. Diet, physical activity, and C-reactive protein (CRP) were measured as well. Carotid IMT was not significant ($p=0.974$) between the groups, with SE values of 0.5945 ± 0.2156 mm, RE at 0.6017 ± 0.1560 mm, and LE at 0.5868 ± 0.1127 mm. Brachial IMT trended towards significance ($p=0.069$) between the groups (SE = 0.3450 ± 0.0528 mm; RE = 0.4163 ± 0.0896 mm; LE = 0.4232 ± 0.0958 mm). Popliteal IMT was not significant ($p=0.127$) between the groups, with the SE values of 0.5669 ± 0.0786 mm, RE at 0.4625 ± 0.0812 mm, and LE at 0.5388 ± 0.1302 mm. Significant differences were observed in MET-min/wk ($p=0.011$; SE = 2225.67 ± 2510.02; RE = 3370.2 ±1136.29;LE = 6039.97 ± 3775.74) and CRP ($p=0.018$; SE = 3.801 ± 4.438 mg/L; RE = 0.885 ± 0.507 mg/L; LE = 0.877 ± 0.609 mg/L) data. When adjusted for MET-min/wk and caloric intake, brachial IMT was significantly different between SE and both RE and LE, and popliteal IMT was significantly different between SE and RE ($p=0.035$ and $p=0.038$ respectively). Based on the findings of this study and previous research, vascular IMT may be related to physical activity, specifically in vascular beds proximal to active muscles, however the relationship may be at least partially dependent upon specific dietary factors.

Introduction

Background

Intima-media thickness (IMT) describes the condition of the inner arterial vessel wall and is associated with several factors of health including body mass, fasting glucose, fasting insulin, as well as diabetes mellitus, coronary artery disease, and cardiac events (Folsom et al, 1994; Ebrahim et al, 1999; Moreau et al, 2006). Of particular research interest is the positive association between increased IMT and risk for atherosclerotic disease. Thickening of the intima-media occurs over time, and significant changes are seen in the 4th or 5th decade of life (Virmani et al, 1991;Ebrahim et al, 1999; Schmidt-Trucksäss et al, 1999; Homma et al, 2001; Tanaka et al, 2002; Moreau et al, 2006). In fact, IMT has been shown to increase two to three fold between the ages of 20 and 90 years (Lakatta et al, 2003; Homma et al, 2001).

Physical activity has been shown to minimize age related increases in IMT, and therefore may decrease the risk for atherosclerotic disease. Moreau et al (2006) found that the age-associated increase in femoral artery IMT was attenuated in middle-aged and older adults who engaged in aerobic-endurance exercise regularly. In addition, Galetta et al (2006) found that carotid IMT was lower in chronically trained runners than in age-matched untrained men. Several other researchers have found an association between physical activity and smaller age-related increases in IMT (Folsom et al, 1994; Dinenno et al, 2001; Lakka et al, 2001; Galetta et al, 2006; Moreau et al, 2006).

Contradicting results have been found when researching the interaction between physical activity and IMT. For example, Tanaka et al (2002) did not find a change in carotid IMT in sedentary subjects who participated in a 3 month aerobic exercise intervention consisting of walking at 60% max heart rate progressing up to 70-75%, while Dinenno et al (2001) found a 13% decrease in femoral IMT in sedentary subjects after a 3 month aerobic exercise intervention consisting of walking or jogging at 65-80% max heart rate. In addition, Galetta et al (2006) found lower common carotid IMT in runners who trained 5-10 hours per week, while Abergel et al (1998) found higher common carotid IMT in professional male cyclists participating in the "Tour de France." Furthermore, both Tanaka et al (2002) and Popovic et al (2010) examined IMT differences among endurance trained athletes and sedentary subjects/non-athletes, and found no significant difference in IMT of the carotid artery. It appears that these inconsistencies may be due to the location of the IMT measurement (e.g. which artery was measured), the type of physical activity used in intervention, and/or the volume of physical activity. Further research is necessary to clarify the impact of long-term exercise training on IMT, and thus risk for atherosclerotic disease, and also if this impact is only seen in the arteries in the exercising limb, or if it is a widespread effect.

Because C-reactive protein (CRP) is a widely used marker of inflammation, researchers have studied the possible relationship between CRP and IMT (Elias-Smale et al, 2007; Sitzer et al, 2002; Makita et al, 2005). Most studies have found significant relationships between carotid IMT and higher levels of CRP, however the relationship lessens or diminishes completely when cardiovascular risk factors are accounted for (Sitzer et al, 2002; Makita et al, 2005). Further research may be able to clarify the relationship between CRP and IMT, and what other factors must be accounted for when observing this relationship.

Purpose of the Study

This study was conducted in order to determine the effect of long term versus recent training on IMT and if this effect is localized in the vascular beds of the tissues directly involved in the activity. To do this, measurements of IMT in sedentary, recently trained, and chronically trained men in the carotid, brachial, and popliteal arteries will be taken. By studying these effects, it can be determined whether or not incorporating moderate/vigorous physical activity into the lifestyle after a prolonged period of sedentary behavior leads to vascular remodeling that is similar to what is seen in chronically active subjects. In addition, CRP will be measured as an indicator of inflammation.

Need for the Study

Research in the past has shown that exercise is an integral part of health and well-being, specifically in preventing and treating cardiac and vascular health. Though there have been conclusions drawn that physical activity can lower IMT, and perhaps lower risk for atherosclerotic disease, the results are varied and somewhat contradictory. This study is aimed at determining first, whether physical activity leads to lower IMT measurements, and further whether previously sedentary subjects who have recently been participating in moderate/vigorous physical activity can see similar lowering effects in IMT as those who have been chronically training for 10 or more years. This should clarify past research and help make future recommendations for physical activity as part of a healthy lifestyle.

Hypotheses

1. IMT in the carotid artery will be significantly higher in the sedentary group as compared to the exercise groups. No significant difference between the recently regular aerobic exercisers and the long-term aerobic exercisers is expected.
2. IMT in the brachial artery will be significantly higher in the sedentary group as compared to the exercise groups. No significant difference between the recently regular aerobic exercisers and the long-term aerobic exercisers is expected.
3. IMT in the popliteal artery will be significantly higher in the sedentary group as compared to the exercise groups. No significant difference between the recently regular aerobic exercisers and the long-term aerobic exercisers is expected.
4. IMT differences between the groups will be the most pronounced in the popliteal artery compared to the brachial and carotid artery.
5. C-reactive protein will be significantly higher in the sedentary group as compared to the exercise groups. There will be no relationship between C-reactive protein and carotid, brachial, and/or popliteal artery IMT.

Assumptions

The following assumptions are made for this study:

1. It is assumed that the subjects are truthful about their level of physical activity and duration of training, such that they are categorized in the correct group.
2. It is assumed that the subjects are truthful about their diet while completing the Diet History Questionnaire.

Delimitations

The following delimitations are made for this study:

1. The participants for this study are men ages 40-60 years old, living in the Shenandoah Valley region of Virginia.

Limitations

1. This study involves a cross-sectional design. Any inferences regarding the effect of exercise training are limited because measurements were not taken before and after an exercise intervention within the same group of subjects.
2. Given that the participants of this study are specifically males between the ages of 40-60 years, the results of the study cannot be generalized to females and those outside these ages.
3. The Diet History Questionnaire is self-reported and based on recall.

Definition of Terms

Intima-medial thickness. The distance from one leading edge of the lumen-intima interface to the leading edge of the media-adventitia interface

Sedentary: Subjects who had not participated in an exercise training program for more than 3 consecutive months during the past 5 years, more than 2 consecutive weeks in the past year, and not at all in the last 3 months; These subjects also have International Physical Activity Questionnaire (IPAQ) results indicating no participation in vigorous activity.

Recent regular aerobic exercisers: Subjects who have participated in moderate to vigorous aerobic activity, based on the IPAQ standards, for an average of 120 minutes per week or more, spread over no less than 3 days per week during the past 6 months to 2 years. They must have participated in 60 minutes per week to be in the IPAQ vigorous activity category, and their mode of exercise actively engaged major muscle groups in the legs and did not engage or only passively engaged major muscle groups in the arms (e.g., cycling, jogging or running). In addition, prior to beginning participation in vigorous activity (2 or more years ago) the prospective subject met the applicable criteria for the sedentary category for at least 5 consecutive years.

Long-term aerobic exercisers: Subjects who have participated in moderate to vigorous aerobic activity, based on the IPAQ standards, for an average of 120 minutes per week or more, spread over no less than 3 days per week during the last 10 years, and they must have participated in 60 minutes per week in the IPAQ vigorous activity category. Also, they have not been "sedentary" for more than 3 consecutive months in any of the last 10 years or for more than 4 consecutive weeks in the last year. In addition, their exercise training must have actively engaged major muscle groups in the legs and did not engage or only passively engaged major muscle groups in the arms (e.g., cycling, jogging or running).

MET-min/wk: A continuous measure of physical activity volume, calculated by weighting types of physical activity (i.e. housework, yardwork, leisure-time) by its energy requirements defined in METs. METs are multiples of the resting metabolic rate and are multiplied by the minutes of activity performed to yield a MET-min score.

Literature Tables

Table 1. Previous studies done on the effect of age on IMT
Cross Sectional Studies

Author	Title	Purpose	Subjects	Artery Measured	Change in IMT	Conclusions
Schmidt-Trucksäss, et al. (Arteriosclerosis Thrombosis, and Vascular Biology, 1999)	Structural, functional, and hemodynamic changes of the common carotid artery with age in male subjects	To examine the relation of aging with alterations of the vascular dimensions of the common carotid artery	9 males between the ages of 16 and 75 years without major atherosclerotic disease	Carotid (a region 2-3 cm proximal to the carotid bulb)	IMT increased 40.4% with age between 20 (0.52 mm) and 60 (0.73 mm) years ($r=0.60$, $p<0.001$)	IMT is mainly determined by the aging process, however it may not be a single noninvasive parameter for the assessment of CAD
Homma, et al. (Stroke, 2001)	Carotid plaque and intima-media thickness assessed by B-Mode ultrasonography in subjects ranging from young adults to centenarians	To examine whether IMT and plaque formation continue to increase through to the eldest age class and whether IMT increases and plaque occurrence are independent of each other	289 subjects aged 21 to 98 years (146 men and 143 women) and 30 centenarians (older than 100 years)	Carotid (Images obtained bilaterally from 40 mm proximal to 30 mm distal to the CCA bifurcation)	IMT increased independently with age in subjects >50 years old ($r=0.75$)	There is a linear correlation between IMT and age suggesting this may be a physiological aging effect; the low plaque prevalence in centenarians suggests that there may be some genetic or acquired characteristics conferring resistance to plaque progression
Virmani, et al. (American Journal of Pathology, 1991)	Effect of aging on aortic morphology in populations with high and low prevalence of hypertension and atherosclerosis	To examine the effects of age on the structural components of the aortic wall	302 male and female cadavers, ages 19-104 years from Australia, China and United States	aorta (from1 cm above the aortic valve annulus to just above the bifurcation of the abdominal aorta)	Intimal thickness increased with age; Medial thickness did not change significantly with age	Intimal thickness increase with age accounts for the well-documented increase in IMT with age; There is a relationship between the increase in intimal thickness and progression of atherosclerotic disease

Table 2a. Previous studies done on the effect of physical activity on IMT

Cross Sectional Studies

Author	Title	Purpose	Subjects	Artery Measured	Physical Activity Measure	Change in IMT	Conclusions
Abergel et al., (American Heart Journal, 1998)	Vascular and cardiac remodeling in world class professional cyclists	To compare carotid artery and left ventricle morphology of world class male cyclists with those of sedentary controls	149 male cyclists (mean age 28.1 ± 3.2 years) participating in the Tour de France; 52 male physicians used as control group (average of 2 years younger than cyclists)	Carotid (Right CCA measured approximately 30 mm proximal to the carotid bifurcation)	Control: Sedentary male physicians except 17 who did regular physical training of 1-25 hr/week, median 6 hr/week; Athletes: Professional cyclists competing in the "Tour de France"	IMT was 13% higher in athletes (0.55 ± 0.05mm in athletes vs. 0.49 ± 0.05mm in controls); ($p<0.0001$)	Cycling training modifies LV morphology as well as CCA dimensions; Author suggested that blood flow to the CCA is increased in response to increased blood flow demand from ECA during cycling
Dinenno et al., (Journal of Physiology , 2001)	Regular endurance exercise induces expansive arterial remodeling in the trained limbs of healthy men	To determine if the training-related differences in lumen diameter previously seen in young adults are also seen in middle-ages and older adults	108 healthy men aged 20-80 years; 53 sedentary subjects and 55 endurance trained (distance runners and/or triathletes)	Femoral (below the inguinal ligament, about 2-3 cm above the bifurcation into the profundus and superficial branches)	Sedentary: Not participating in regular exercise; Endurance trained: distance runners and/or triathletes training heavily and competitive in local races	IMT was 14% lower in Endurance trained group compared to Sedentary group (0.46 ± 0.02mm vs. 0.55 ± 0.02mm); ($p<0.001$)	Femoral artery lumen diameter is greater and IMT is smaller in endurance leg-trained athletes compared to sedentary health men across the ages
Ebrahim et al., (Stroke, 1999)	Carotid plaque, intima media thickness, cardiovascular risk factors, and prevalent cardiovascular disease in men and women: The British Regional Heart Study	To clarify the relationships between cardiovascular risk factors, common carotid IMT, bifurcation IMT, and plaques	Male participants from British Regional heart Study and random sample of women of similar age (56-77 years); 425 men and 375 women	Carotid (at the thickest point on the distal wall of the CCA about 1.5 cm proximal to the flow divider; also measures at the point at which th arterial wall diverged to form the bulb)	Completed self-administered questionnaire which classified sporting activity as none, occasional, or frequent	There was no significant relationship between IMT and physical exercise (0.83 ± 0.01mm for "none", 0.84 ± 0.04mm for "occasional", and 0.86 ± 0.02mm "frequent")	There is a strong correlation between IMT and both age and BP. The association between thicker IMT and prevalence of plaques supports idea that IMT is related to atherosclerosis.
Folsom et al., (Stroke, 1994)	Relation of carotid artery wall thickness to diabetes mellitus, fasting glucose and insulin, body size, and physical activity.	To examine the relation of carotid artery wall thickness with diabetes, fasting insulin and hyperglycemia, body shape and size, and physical activity	14,430 adults aged 45- 64 years, free of symptomatic CVD	Carotid (divided into three segments: the distal 1 cm straight portion of the CCA, the carotid bifurcation, and the proximal 1 cm portion of the ICA)	Assessed through questionnaire developed by Baecke (16 items about usual exertion and three indexes ranging from low (1) to high (5) derived for physical activity at work, during leisure time, and during work)	IMT decreased with increasing physical activity at work (decrease of about 0.006 to 0.010 mm per unit increase in work index); ($p=.03$)	Greater BMI, W/H, less physical activity, greater fasting glucose/insulin, and diabetes are all related to prevalent CVD and these factors are similarly associated with greater carotid artery wall thickness

Table 2a. cont. Previous studies done on the effect of physical activity on IMT

Cross Sectional Studies

Author	Title	Purpose	Subjects	Artery Measured	Physical Activity Measure	Change in IMT	Conclusions
Galetta et al., (Atherosclerosis , 2006)	Endothelium-dependent vasodilation and carotid artery wall remodeling in athletes and sedentary subjects	To examine whether aging is associated with increased vascular structural alterations in healthy subjects	32 male athletes and 32 age and sex matched healthy sedentary subjects (mean age 48 ± 19 years)	carotid (distal segment of the right and left CCA)	Athletes: VO2max greater than 50 ml/kg/min who performed long distance running 3 days/week and brisk walking, dumbbell training 2 days/week, and did a mid-long distance race every 2 weeks; Sedentary: VO2max less than 45 ml/kg/min	IMT was lower in older athletes than in older sedentary subjects ($p<0.0001$)	EDD was inversely related to carotid artery IMT and C-IBS values, which supports the possibility that in aging, functional and structural changes interact to determine vascular alterations
Lakka et al., (Annals of Internal Medicine, 2001)	Cardiorespiratory fitness and the progression of carotid atherosclerosis in middle-ages men	To examine the relationship between cardiorespiratory fitness and the progression of early carotid atherosclerosis	854 men aged 42-60 years (part of Kuopio Ischemic Heart Disease Risk Factor Study	Carotid (section at the distal end of the left and right CCA proximal to the carotid bulb)	Used maximal oxygen uptake (cycle ergometer) and the KIHD 12-Mnth Leisure-Time Physical Activity History questionnaire	IMT increased with decreasing VO2max (0.834mm for <26.1 mL/kg/min compared to 0.697mm for >36.2 mL/kg/min) $p<0.001$	Low cardiorespiratory fitness (as assessed by VO2max) is a strong risk factor for the progression of carotid atherosclerosis
Moreau et al., (European Journal of Cardiovascular Prevention and Rehabilitation, 2006)	Habitual aerobic exercise is associated with smaller femoral artery intima-media thickness with age in healthy men and women	To determine if the age-related increase in common femoral artery IMT is smaller in endurance exercise-trained compared with sedentary healthy adults	173 healthy men aged 20-39 years (young), 40-59 years (middle-aged), and 60-79 years (older)	Femoral (right common femoral artery)	Sedentary: no regular physical activity; Moderately aerobically active: light to moderate intensity exercise ≥3 days/wk; Endurance trained: vigorous aerobic endurance exercise ≥5 days/wk and competing in local road races	IMT of endurance trained group was about 20-27% smaller than in sedentary group and tended to be smaller than in moderately active men ($p=0.056$)	Femoral artery IMT increases with age regardless of physical activity; Those who are endurance trained and moderately aerobically active see smaller age-related increases than those who are sedentary
Popovic et al., (The American Journal of the Medical Sciences, 2010)	The effects of endurance and recreational exercise on subclinical evidence of atherosclerosis in young adults	To identify the respective effects of endurance exercise, recreational exercise and sedentary lifestyle on traditional cardiovascular risk factors and IMT	150 men and women aged 20 and 40 years (50 endurance athletes, 50 recreational athletes and 50 nonexercising men and women)	carotid (right CCA below the bifurcation of the ECA)	Endurance athlete: performs 3 or more hr/week of running and/or cycling and/or swimming consistently for a minimum of 6 months; Recreational athlete: performs 3 or more hr/week of general sports; Nonathletes: performed less than 3 hr/week of sports or general exercise	No significant difference in IMT between any of the exercise groups and sedentary group	Physical activity shows positive effects on the risk profile for atherosclerotic disease in young, healthy adults, however, there is not statistically significant influence on vascular wall measures

Table 2a. cont. Previous studies done on the effect of physical activity on IMT

Cross Sectional Studies

Author	Title	Purpose	Subjects	Artery Measured	Physical Activity Measure	Change in IMT	Conclusions
Tanaka et al. (Journal of Applied Physiology, 2002)	Regular aerobic exercise and the age-related increase in carotid artery intima-media thickness in healthy men	Determine the possible influence of regular aerobic exercise on the age-related increase in carotid artery IMT	137 healthy men grouped by age (young=18-37, middle-aged=38-57, older=58-77)	Carotid (obtained at the proximal 1 to 2 cm straight portion of the common carotid artery)	Sedentary: no regular physical activity; Endurance trained: vigorous endurance exercise >5 times per week and active in local road running races	IMT was not significantly different between the sedentary and endurance trained groups	IMT increases with age and regular vigorous endurance exercise does not attenuate the age related increase; May be because exercise did not affect age related elevation in carotid BP
Moreau, K.L., Donato, A.J., Seals, D.R., Dinenno, F.A., Blackett, S.D., Hoetzer, G.L., Desouza, C.A., and Tanaka, H. (American Journal of Physiology-Heart and Circulatory Physiology, 2006)	Arterial intima-media thickness: site-specific associations with HRT and habitual exercise	To determine the association between HRT and IMT, as well the association between habitual aerobic exercise and IMT	77 healthy post-menopausal women (43 sedentary and 34 endurance trained)	carotid and femoral	Endurance trained: perform regular aerobic exercise an average of 58 min per day, 5.1 days per week for at least 5 years and active in loacl road races	femoral: diameter was larger in endurance trained, IMT was smaller in the endurance trained groups and the sedentary HRT group compared to the sedentary no HRT group; carotid: IMT was not significantly associated with training	endurance training and HRT status are associated with smaller IMT, evident in muscular arteries

Table 2b. Previous studies done on the effect of physical activity on IMT

Experimental Studies

Author	Title	Purpose	Subjects	Artery Measured	Physical Activity Intervention	Change in IMT	Conclusions
Dinenno et al. (Journal of Physiology, 2001)	Regular endurance exercise induces expansive arterial remodeling in the trained limbs of healthy men	To determine if moderate endurance training can induce femoral artery remodeling in previously sedentary adults differing in age in the absence of changes to atherosclerotic risk factors	22 previously sedentary men aged 31-73 years	Femoral (below the inguinal ligament, about 2-3 cm above the bifurcation into the profundus and superficial branches)	Walking and/or jogging 5-7 days/week, 40-50 min/day, at 65-80% MHR for an average of 13.5 weeks	IMT decreased 13 % with the exercise intervention (0.65 ± 0.05mm before to 0.56 ± 0.05mm after)	Three months of regular moderate intensity leg exercise decreases femoral IMT in previously sedentary men independent of age and independent of improvements in atherosclerotic risk factors
Tanaka et al., (Journal of Applied Physiology, 2002)	Regular aerobic exercise and the age-related increase in carotid artery intima-media thickness in healthy men	Determine the possible influence of regular aerobic exercise on the age-related increase in carotid artery IMT	18 middle aged and older subjects who were sedentary (average age of 54 ± 2 years)	Carotid (obtained at the proximal 1 to 2 cm straight portion of the common carotid artery)	Initial: walking 25-30 min/day, 3-4 days/week at about 60% MHR; Progression: walking/jogging 40-45 min/day, 4-6 days/week, at about 70-75% MHR	IMT did not change in response to aerobic exercise intervention	IMT increases with age independent of a sedentary lifestyle and a 3 month aerobic exercise intervention does not affect carotid IMT. Exercise may not affect IMT because it does not affect age related elevation in carotid BP

Table 3. Previous studies done on the relationship between c-reactive protein and IMT

Author	Title	Purpose	Subjects	Artery Measured	Results	Conclusions
Elias-Smale, S.E., Kardys, I., Oudkerk, M., Hofman, A., and Witteman, J.C.M. (Atherosclerosis , 2007)	C-reactive protein is related to extent and progression of coronary and extra-coronary atherosclerosis; results from the Rotterdam study	To study the association between CRP and the extent and progression of atherosclerosis	7983 men and women >55 years old	CCA	Strong, graded increase in CRP levels observed with higher number of carotid plauqes; CRP levels rose across the highest 3 deciles of carotid IMT (IMT>0.86 mm)	CRP is independently related to higher levels of carotid IMT, but CRP association with change in IMT is not significant; IMT may represent early stages of atherosclerosis
Sitzer, M., Markus, H.S., Mendall, M.A., Liehr, R., Knorr, U., and Steinmetx, H. (Journal of Cardiovascular Risk, 2002)	C-reactive protein and carotid intimal medial thickness in a community population	To determine if elevated CRP is involved in initiating and promoting atherogenesis or whether it is only a reflection of the presence of subclinical atherosclerosis	1018 men and women aged 30-75 years (mean age 54.1)	CCA, carotid bifurcation and ICA	Positive, linear relationship between increasing CRP and increased IMT in all arterial sites. This relationship is lessened, but still significant when risk factors are accounted for. Relationship does not exist when fibrinogen is controlled for.	CRP is positively correlated with early arteriosclerosis (defined by intima-medial thickening), however the association is weakened when risk factors are controlled for. CRP may mediate the effect of risk factors and in that way promote atherogenesis.
Makita, S., Nakamura, M., and Hiramori, K. (Stroke, 2005).	The association of c-reactive protein levels with carotid intima-media complex thickness and plaque formation in the general population	To identify which atherosclerotic changes are associated with the inflammation and to determine if these relationships are common to both genders	2056 men and women (mean age 58.3 years)	CCA	There is a significant relationship between carotid IMT and elevated CRP in both men and women, which disappears when adjusted for age and cardiovascular risk factors. Elevated CRP is significantly related to carotid plaque presence in men.	There is an association between elevated CRP and carotid atherosclerosis in men, although the relationship between IMT and CRP appears to be dependent on age and cardiovascular risk factors. There does not appear to be a relationship between elevated CRP and carotid atherosclerosis in women

Table 4. Previous studies done on the relationship between c-reactive protein and physical activity

Author	Title	Purpose	Subjects	Physical Activity	Results	Conclusions
Ford, E.S. (Epidemiology, 2002)	Does exercise reduce inflammation? Physical activity and c-reactive protein among U.S. adults.	To determine the association between physical activity and C-reactive protein	13,748 male and female participants older than 20 years	Categorized as vigorously active, moderately active, lightly active and sedentary based on self-reported physical activity questionnaire	C-reactive protein and physical activity were associated; OR for lightly active was 0.78, for moderately active was 0.59, and vigorously active was 0.30 compared with sedentary	Physical activity is inversely associated with C-reactive protein, suggesting that physical activity may lessen inflammation
Lakka, T.A., Lakka, H., Rankinen, T., Leon, A.S., Rao, D.C., Skinner, J.S., Wilmore, J.H., and Bouchard, C. (European Heart Journal, 2005)	Effect of exercise training on plasma levels of c-reactive protein in healthy adults: the HERITGAE family study	To determine the effect of exercise training on c-reactive protein	652 sedentary, healthy white and black men and women	20 week exercise program of 3 cycle ergometer session per week (progressing from 30 min per session to 50 min per session and from 55% VO2max to 75%)	C-reactive protein dropped a median of 1.34 mg/L in the high baseline CRP group and was significant across patient populations	C-reactive protein can be reduced through exercise training in adults with high CRP levels, which may explain why exercise training is affective in treating cardiovascular disease
Mattusch, F., Dufaux, B., Haine, O., Mertens, I., and Rost, R. (International Journal of Sports Medicine, 2000)	Reduction of the plasma concentration of c-reactive protein following nine months of endurance training	To determine if training suppresses the inflammatory response to exercise and if training reduces CRP	14 subjects training for a marathon	running; distance per week increased from 31 km to 53 km through 8 months of training	CRP median was reduced from 1.19 mg/L to 0.82 mg/L after training ($p<.05$)	Intensive regular exercise training has a systemic anti-inflammatory effect

Literature Table Summaries

The Effect of Age on IMT

Several studies have shown that artery IMT increases with age (Virmani et al, 1991; Ebrahim et al, 1999; Schmidt-Trucksäss et al, 1999; Homma et al, 2001; Tanaka et al, 2002; Galetta et al, 2006; Moreau et al, 2006). Notably, Schmidt-Trucksäss et al (1999) studied the alterations to vascular dimensions of the common carotid artery with aging. They found that between the ages of 20 and 60 years, the IMT of males in the study increased 40.4%. Homma et al (2001) examined the relationship between IMT and increasing age, and found a linear increase between the two. Studying subjects ages 21 to 98 years, the researchers found that age was the only factor independently related to increased IMT. While studying the aorta of male and female cadavers, Virmani et al (1991) also discovered a positive, linear relationship between aortic IMT and increasing age. These researchers also concluded that there was a relationship between increasing aortic IMT and atherosclerotic disease. Several other researchers have discovered a relationship between IMT and age while studying the affects of physical activity on age (Ebrahim et al, 1999; Tanaka et al, 2002; Galetta et al, 2006; Moreau et al, 2006). Tanaka et al (2002) also found that carotid IMT in both sedentary and trained subjects were progressively higher with age. Lakatta and Levy (2003) studied cardiac aging and found that artery wall thickening, specifically intimal thickening, occurs during aging and that IMT can increase two or three fold between the ages of 20 and 90 years. The associations between age and IMT in both the common carotid artery and the bifurcation were demonstrated by Ebrahim et al (1999). They also found that IMT of the common carotid artery was also associated with risk factors for stroke, and IMT of the bifurcation was associated with heart disease risk factors and ischemic heart disease. Although researchers have found lower IMT in endurance subjects than in age-matched sedentary subjects, independent of training status, IMT appears to increase with age (Galetta et al, 2006; Moreau et al, 2006).

The Effect of Physical Activity on IMT: Cross Sectional Studies

Researchers examining the relationship between IMT and physical activity have found lower IMT measures in subjects who are physically active (Folsom et al, 1994; Abergel et al, 1998; Ebrahim et al, 1999; Dinenno et al, 2001; Lakatta et al, 2001; Tanaka et al, 2002; Galetta et al, 2006; Moreau et al, 2006; Popovic et al, 2010). When describing the relationship between cardiovascular risk factors and IMT, Folsom et al (1994) found that IMT decreased with increasing levels of physical exertion assessed by a physical activity questionnaire by Baecke. This relationship was independent of any other major risk factors. Comparing IMT of highly-trained endurance athletes with sedentary subjects had yielded similar results as well. Galetta et al (2005) studied runners who trained 1-2 hours daily, 5 days per week, whose training program consisted of 3 days of long distance running, and 2 days of weight training with dumbbells. They found that these athletes had lower IMT values than their sedentary peers, and the difference in IMT between younger and older subjects seen in sedentary subjects was blunted by chronic endurance exercise in the endurance trained subjects. Moreau et al (2006) studied men aged 20-79 years old and in three activity classes: sedentary, moderately aerobically active (light to moderate intensity exercise 3 or more times per week), and endurance exercise-trained (vigorous aerobic-endurance exercise 5 or more times per week and competing in local road running races). They also found that IMT was smaller (20-27%)

in age-matched, endurance trained men compared with sedentary men. Furthermore, they also found a trend in IMT to be smaller in age-matched, moderately active compared with sedentary men. Like Galetta et al (2005), the researchers found the age-associated increases in IMT were smaller among the active subjects compared with the sedentary subjects (Moreau et al, 2006).

However, there are a few studies that found contradictory results (Abergel et al, 1998; Ebrahim et al, 1999; Tanaka et al, 2002; Popovic et al, 2010). While studying male cyclists participating in the "Tour de France," Abergel et al (1998) found that both mean arterial diameter and mean arterial diastolic intima-media thickness of the carotid artery were 13% higher in the cyclists than in the control subjects. They hypothesized that this may be the result of increased artery wall sheer stress due to increased blood flow during exercise. Also studying carotid IMT, Ebrahim et al (1999) found no significant difference in IMT between subjects who did no, occasional, and frequent physical activity as self reported on a questionnaire. Furthermore, both Tanaka et al (2002) and Popovic et al (2010) studied the carotid artery IMT in non-athletes/sedentary and endurance trained groups and found no significant differences in IMT. In conclusion, there is research to back up claims that physical activity can increase, decrease, or not affect IMT, however there are inconsistencies in the methodologies of the past research on the topic.

The Effect of Physical Activity on IMT: Experimental Studies

There has been limited experimental research done on the affect of physical activity on IMT, however even within this limited field of research, there are inconsistencies. Dinenno et al (2001) did find that both femoral artery IMT and IMT/lumen ratio were smaller in subjects after exercise training. Specifically, researchers asked subjects to walk or jog 5-7 days per week, 40-50 minutes per day at 5-80% of their individual maximum heart rate determined during maximal exercise testing (Dinenno et al, 2001). However, Tanaka et al (2002) performed both a cross-sectional and longitudinal study, neither of which yielded significant relationship between IMT and regular aerobic exercise. In the experimental study, previously sedentary subjects who participated in a 3 month exercise intervention, did not see significant IMT changes in the carotid artery after training (Tanaka et al, 2002). This training consisted of 25-30 minutes of walking, 3-4 days per week at about 60% of their maximal heart rate, which then progressed as their exercise tolerance improved, to 40-45 minutes of walking/jogging, 4-6 days per week, at 70-75% of their maximal heart rate. As with the cross sectional studies on this topic, the methodologies used in these studies are inconsistent and further research of this nature is needed to clarify the affect of a physical activity intervention on IMT in previously sedentary subjects.

The Relationship Between C-Reactive Protein and IMT

According to previous literature, C-Reactive Protein (CRP) may be related to carotid artery IMT, however the relationship has yet to be clarified. Specifically, Elias-Smale et al (2007) studied the association between CRP and progression of atherosclerosis by measuring carotid artery IMT, and found that although CRP was not significantly associated with change in IMT, CRP levels did rise across the highest 3 deciles of IMT, suggesting that higher IMT levels may be associated with early stages of atherosclerosis indicated by higher levels of CRP. Sitzer et al (2002) also suggested that CRP is positively correlated with early arteriosclerosis as measured by IMT, however when controlled for cardiovascular risk factors, the correlation was weakened. This may indicate that higher CRP levels may mediate the effect of cardiovascular risk factors, and in that way promote atherogenesis. Additionally, Makita et al (2005) found a significant relationship between carotid IMT and elevated levels of CRP, which disappeared when adjusted for cardiovascular risk factors. Therefore, it appears that there may be some relationship between CRP and carotid IMT, however there is a potential role of cardiovascular risk factors in this relationship.

The Relationship Between C-Reactive Protein and Physical Activity

Previous literature has reported a well establish relationship between physical activity and CRP. Ford (2002) suggested that physical activity may lessen inflammation based off study results indicating lower CRP levels in subjects who reported being lightly, moderately, and vigorously active based on self-reported physical activity questionnaires. Mattusch et al (2000) and Lakka et al (2005) reported decreases in CRP after exercise training interventions. Lakka et al (2005) found that CRP dropped a median of 1.34 mg/L in patients with high baseline CRP (>3.0 mg/L) after a 20 week cycle ergometer exercise intervention. Mattusch et al (2000) studied 14 subjects before and after marathon training to determine if CRP would decrease after training despite the potential inflammatory effect of high levels of training, and found that CRP was significantly reduced after the training program. It appears that both cross-sectional and experimental data point to an inverse association between physical activity and CRP.

Subjects and Methods

Subjects

Thirty-five male subjects between 40 and 60 years old were recruited from JMU and the greater community by “word-of-mouth”. Potential subjects were given a brief description of the study including selection criteria, direct time commitment, as well as the risks and benefits of participation. Female subjects were not included because they are less subject to changes in IMT associated with physical activity prior to menopause. Methods for the study were approved by the James Madison University Institutional Research Board prior to commencement.

All prospective subjects were screened for participation based on specific inclusion guidelines (see Appendix A) for classification into one of the following groups: 1) sedentary (SE), 2) recent regular aerobic exercise (RE), and 3) long term aerobic exercise (LE).

Sedentary subjects (SE)

These subjects had not participated in an exercise training program for more than 3 consecutive months during the past 5 years, more than 2 consecutive weeks in the past year, and not at all in the last 3 months. They also had IPAQ results indicating no participation in vigorous activity.

Recent regular aerobic exercisers (RE)

These subjects had participated in moderate to vigorous aerobic activity, based on the IPAQ standards, for an average of 120 minutes per week or more, spread over no less than 3 days per week during the 6 months to 2 years prior to data collection. They had participated in 60 minutes per week in the IPAQ vigorous activity category, and their mode of exercise actively engaged major muscle groups in the legs and did not engage or only passively engaged major muscle groups in the arms (e.g., cycling, jogging or running). In addition, prior to beginning participation in vigorous activity (2 or more years ago) the prospective subject had met the applicable criteria for the sedentary category for at least 5 consecutive years.

Long term aerobic exercisers (LE)

These subjects had participated in moderate to vigorous aerobic activity, based on the IPAQ standards, for an average of 120 minutes per week or more, spread over no less than 3 days per week during the 10 years prior to data collection, and they had participated in 60 minutes per week in the IPAQ vigorous activity category. Also, they were not “sedentary” for more than 3 consecutive months in any of the previous 10 years or for more than 4 consecutive weeks in the year prior to data collection. In addition, their exercise training actively engaged major muscle groups in the legs and did not engage or only passively engaged major muscle groups in the arms (e.g., cycling, jogging or running).

Methodology

All subjects who met the inclusion criteria for one of the three categories reported to the Human Performance Labs in Godwin Hall (Room #209) for activity screening, health screening, ultrasound measures and exercise testing. The heath screening included blood pressure assessment and completion of the AHA/ACSM Health/Fitness Facility Preparticipation Screening Questionnaire (see Appendix B) to determine if they had any health impairments that were contraindications for exercise testing. Prospective subjects who had two or more cardiovascular risk factors, or those who had any history, symptoms, or other health issues were required to have their physician sign a consent form (see Appendix C) before participating in data collection.

Dietary Analysis

In order to account for dietary factors that may be related to IMT, participants completed a web-based version of the National Cancer Institute's Diet History Questionnaire (Diet History Questionnaire, Version 1.0. National Institutes of Health, Applied Research Program, National Cancer Institute. 2007). This data was used to evaluate historical total caloric intake as well as intake of fats, carbohydrates, protein, cholesterol, sodium and other nutrients.

International Physical Activity Questionnaire

Average MET-min/wk was assessed using the International Physical Activity Questionnaire (see Appendix D). The data was then be divided by intensity to report moderate MET-min/wk and vigorous MET-min/wk.

Venous blood sample

A single, resting 10 mL venous blood sample from an antecubital vein was taken prior to ultrasound and maximal oxygen uptake measurements. The whole blood sample sat at room temperature for 30 minutes, then was centrifuged in a refrigerated centrifuge for 20 minutes at 4000 rpm. Serum was extracted and frozen at -80° C until analyzed. C-reactive protein analysis was carried out by high sensitivity enzyme immunoassay in accordance with the procedures defined by Oxis International (Oxis Research, Foster City, CA).

Ultrasound Measurements

Right side carotid, above the elbow brachial, and above the knee popliteal IMT were measured from images derived from an ultrasound machine (Mindray, DC-6, Mahwah, NJ). Ultrasound measurement sites and procedures are previously described in Zwiebel and Pellerito's Introduction to Vascular Ultrasonography, 2004. IMT was defined as the distance from one leading edge of the lumen-intima interface to the leading edge of the media-adventitia interface. All ultrasound measurements preceded exercise testing. Specific IMT measurements were conducted using ImageJ software (National Institute of Health) and measured perpendicular to the vessel wall.

Exercise Testing Protocol

Peak oxygen consumption was used as a measure of maximal aerobic capacity and fitness. Subjects performed a graded exercise test on a cycle ergometer to determine maximal oxygen uptake (VO_{2peak}). ACSM protocol for the YMCA bike test was followed (ACSM, 2010). It was assumed that VO_{2peak} was achieved if one or more of the following were met: visual plateau in VO_2, RER ≥ 1.00, and/or volitional fatigue. In addition, the test was terminated if subjects presented any of ACSM's general indications for stopping an exercise test (ACSM, 2010). This protocol was chosen because it accommodates differences in response to an initial load. With the wide range in fitness levels of the subjects, this protocol allowed the subsequent loads to better match the fitness of each subject and ensure a valid test.

Statistical Analysis

This study employed a cross-sectional, single-blind design that compared IMT between sedentary, recent aerobically active and long-term aerobically active subjects. Preliminary analysis included a 1 x 3 ANOVA with 1 between factor (activity group). The data is presented as mean +/- standard deviation and an alpha level of .05 was established for statistical significance.

Upon completing the data collection, the group sample sizes were 10, 8 and 17 for the sedentary, recent aerobically active and long-term active groups, respectively. Given the small samples, the Shapiro-Wilk test for normality was carried out on the IMT data. The analysis indicated that the sample distributions for the IMT data did not significantly deviate from the normal distribution and therefore the ANOVA procedure was used.

Test-retest analysis was conducted on an independent sample ($n = 7$) in order to evaluate the researcher's IMT measurement reliability. Evaluation of the test-retest data yielded the following results. Pre and post carotid IMT measurements were significantly correlated ($r=0.99$, $p < 0.001$) not significantly different ($t=1.131$, $p=0.301$) and the coefficient of variation (COV) was 3.18%. Brachial IMT measurements were significantly correlated ($r=0.962$, $p < 0.001$) not significantly different ($t=0.0$, $p=1.0$) and the COV was 2.36%. Popliteal IMT measurements were significantly correlated ($r=0.965$, $p < 0.001$) not significantly different ($t=0.505$, $p=0.631$) and the COV was 1.82%.

Results

A total of 35 individuals (aged 49.69 ± 6.48 years) were included in the analysis, distributed over 3 groups that were categorized as long-term aerobic exercisers (LE; n=17), recent aerobic exercisers (RE; n=8), and sedentary (SE; n=10). Demographic data for the 3 groups are shown in Table 1. No significant differences were found between the groups for age (p=0.247) and height (p=0.160); however, weight (p=0.002) and BMI (p=0.005) were significantly different between SE and the two exercise groups. VO_{2peak} (p=0.000) and total MET-min/wk (p=0.011) were both significantly different between SE and the two exercise groups. When separated by intensity, moderate MET-min/wk were 1636.5 ± 2039.1 for SE, 1117.7 ± 958.78 for RE, and 1251.76 ± 1334.28 for LE, while vigorous MET-min/wk were 648 ± 1324.67 for SE, 1579.13 ± 973.97 for RE and 3656.47 ± 2123.67 for LE. No significant differences in systolic (p=0.488) or diastolic (p=0.084) blood pressure were observed.

	SE	RE	LE
Age (yrs)	48.5 ± 5.28	47.25 ± 5.83	51.53 ± 7.16
Height (m)	1.799 ± 0.11	1.8125 ± 0.05	1.7553 ± 0.07
Weight (kg)	95.908 ± 22.62[ab]	81.533 ± 7.08[a]	73.072 ± 10.09[b]
BMI (kg/m^2)	29.805 ± 7.49[ab]	24.795 ± 1.61[a]	23.6565 ± 2.41[b]
VO_{2peak} (ml/kg/min)	29.01 ± 9.69[ab]	42.4429 ± 5.67[a]	53.9294 ± 8.17[b]
MET-min/wk	2225.67 ± 2510.02[b]	3370.2 ± 1136.29	6039.97 ± 3775.74[b]
Systolic BP (mmHg)	131.4 ± 12.47	126.5 ± 10.46	125.875 ± 10.81
Diastolic BP (mmHg)	89.8 ± 13.31	81 ± 9.13	82.9375 ± 3.89

Table 5. Demographic means ± standard deviation; [a] denotes p<0.05 between SE and RE; [b] denotes significant difference between SE and LE.

There were no significant differences between the groups in total caloric intake (p=0.367), percent energy from carbohydrates (p=0.562), percent energy from protein (p=0.851), or percent energy from fat (p=0.412).

	SE	RE	LE
Total Kcal	2104.98 ± 712.55	1739.03 ± 605.37	2241.24 ± 939.53
% Energy from CHO	51.53 ± 14.12	50.3 ± 5.34	54.33 ± 7.38
% Energy from PRO	14.93 ± 2.70	15.28 ± 2.19	14.76 ± 1.74
% Energy from FAT	33.06 ± 9.51	34.19 ± 4.01	30.7 ± 5.16

Table 6. Dietary means ± standard deviation

Carotid IMT was not significant (p=0.974) between the groups, with SE mean at 0.5945 ± 0.2156 mm, RE mean at 0.6017 ± 0.1560 mm, and LE mean at 0.5868 ± 0.1127 mm. Brachial IMT trended towards significance (p=0.069) between the groups with the SE mean at 0.3450 ± 0.0528 mm, RE mean at 0.4163 ± 0.0896 mm, and group LE at 0.4232 ± 0.0958 mm. Popliteal IMT was not significant (p=0.127) between the groups, with the SE mean at 0.5669 ± 0.0786 mm, RE mean at 0.4625 ± 0.0812 mm, and LE mean at 0.5388 ± 0.1302 mm.

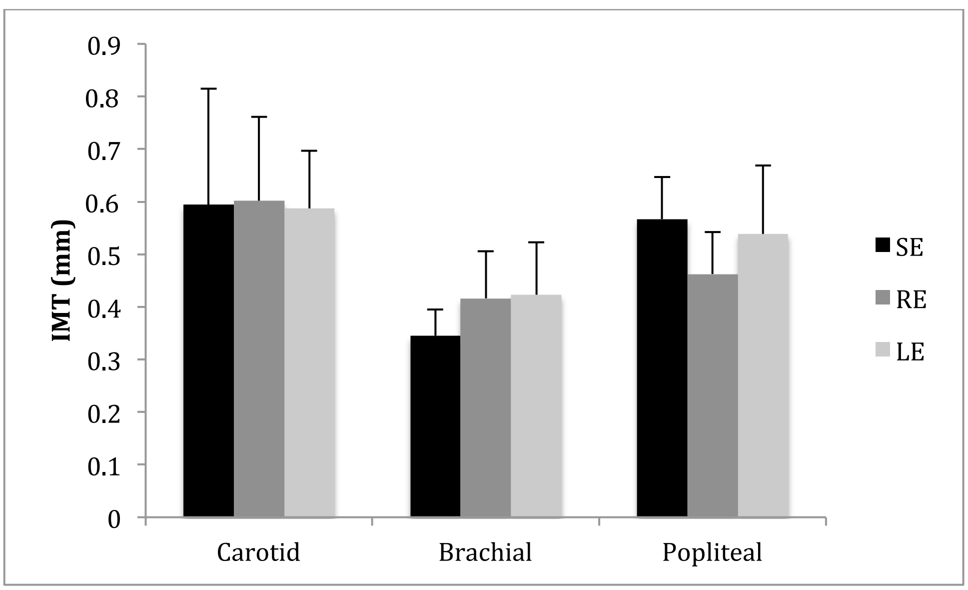

Figure 1. Carotid, brachial, and popliteal artery IMT measurements for the SE, RE, and LE groups

CRP was significantly higher ($p=0.018$) in SE (3.801 ± 4.438 mg/L), when compared to RE (0.885 ± 0.507 mg/L) and LE (0.877 ± 0.609 mg/L).

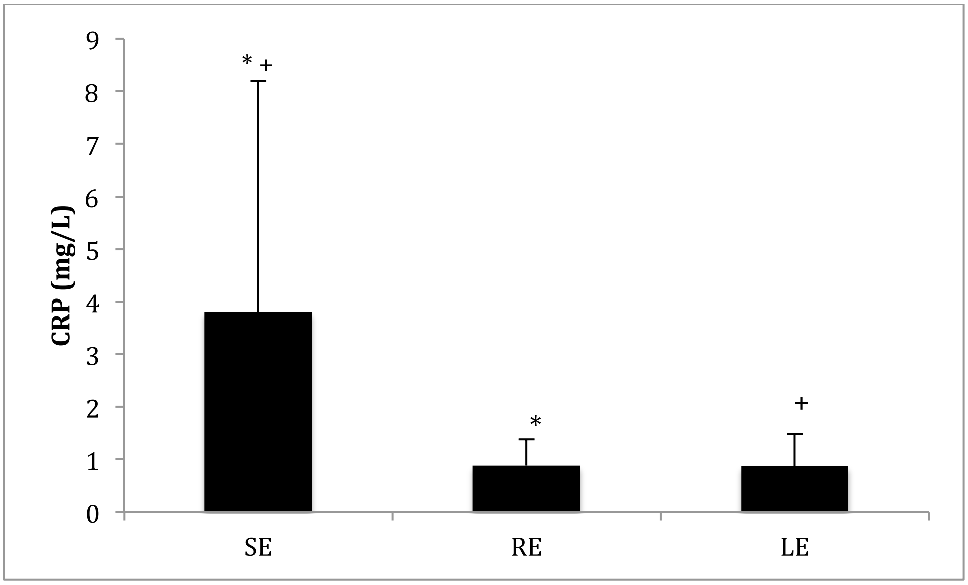

Figure 2. Mean CRP values for the SE, RE, and LE groups; * denotes p<0.05 between SE and RE; + denotes p<0.05 between SE and LE

Discussion

The current study examined intima-media thickness of the carotid, brachial, and popliteal arteries. The carotid artery is large, easy to locate, and has been used widely in previous research examining potential variables for fluctuation in IMT (Folsom et al., 1994; Abergel et al., 1998; Ebrahim et al., 1999; Schmidt- Trucksäss et al., 1999; Homma et al., 2001; Lakka et al., 2001; Tanaka et al., 2002; Galetta et al., 2006; Popovic et al., 2010). The brachial and popliteal arteries were chosen as comparison arteries to examine the potential effect of active and passive muscle groups on vascular structure. Billinger et al (2009) saw significant improvements in femoral artery peak flow and diameter in the hemiparetic leg of stroke patients after single leg exercise, while no improvements were seen in the other, non-exercised limb. This may indicate that vascular changes are enhanced by physical activity of proximal muscles.

When examining the carotid artery, IMT was expected to be higher in the sedentary group as compared to the exercise groups. A significant difference between the two groups of exercisers was not expected. No significant differences were found between the groups in carotid artery IMT ($p=0.974$). Although previous research done on the relationship between physical activity and carotid IMT is inconsistent, these finding do agree with some previous literature (Ebrahim et al, 1999; Tanaka et al, 2002; Popovic et al, 2010). Ebrahim et al (1999) found no significant relationship between carotid IMT and physical activity frequency self reported by men and women aged 56-77 years. Additionally, both Tanaka et al (2002) and Popovic et al (2010) failed to find significant differences between carotid IMT in endurance athletes as compared to non-athletes.

Contradictory to the current study, other researchers have established a link between carotid IMT and physical activity (Folsom et al, 1994; Lakka et al, 2001; Galetta et al, 2006). Folsom et al (1994) found a significant decrease of 0.006-0.010 mm in carotid IMT per unit work increase on a self-reported questionnaire on physical activity at leisure time and during work. Galetta et al (2006) compared carotid IMT in endurance athletes and sedentary men based on both physical activity and maximal oxygen consumption. Their classifications by maximal oxygen consumption do agree with the VO_{2peak} data we collected for our exercisers and non-exercisers, however Galetta et al (2006) found a significant difference between the carotid IMT values for each group, while we failed to find such a relationship. Lakka et al (2001) researched the relationship between VO_{2max} values and carotid IMT, and found that IMT values increased significantly with decreasing VO_{2max} values. We did find a significant difference in VO_{2peak} values between the groups ($p=0.000$), however we did not see a corresponding difference or relationship in carotid IMT.

Conclusions drawn by Seals et al (2008), agree with past findings, as well as the finding of the current study that carotid artery IMT is not associated with exercise habits. Tanaka et al (2001) found that carotid artery pressure is a strong predictor of carotid IMT, however carotid artery pressure has not been found to be associated with physical activity habits (Miyachi et al, 2003; Moreau et al, 2002). Thus, a decreased in carotid IMT with increasing physical activity should not be expected, nor should it be the standard to which the current study is compared.

In order to compare extremities in which the musculature is actively engaged in the exercise as opposed to passively engaged, IMT between the groups in the brachial (passive) and popliteal (active) arteries were compared. IMT in the brachial and popliteal arteries was expected to be significantly higher in the sedentary group as compared to the exercise groups. No significant difference between RE and LE was expected. No significant difference was found between the groups in popliteal artery IMT (p=0.127), however difference between SE brachial artery IMT and both RE and LE brachial IMT trended toward significance (p=0.069).

Most research done on the relationship between IMT and physical activity has been done on the carotid artery, however there has been some research focused on leg artery IMT, most of which examines the femoral artery (Dinenno et al, 2001; Moreau et al, 2006). The results of the current study do not agree with the findings these studies. Dinenno et al (2001) did both cross sectional and experimental research, and found 14% lower femoral IMT values in endurance trained men as compared to their sedentary counterparts, and found an average 13% decrease in femoral IMT in men aged 31-73 years after a 3 month exercise intervention. Moreau et al (2006) found 20-27% lower femoral IMT values in endurance-trained men as compared to sedentary men, and they found a trend towards significance when comparing femoral IMT in moderately active men and in sedentary men (p=0.056).

According to by Seals et al (2008), changes in arteries of exercising limbs are expected based on the theory that the arteries in these limbs go through remodeling in order to normalize wall sheer stress brought on by increased blood flow from exercise (Dinenno et al, 2001). Although the current study failed to find significant differences between the groups in the peripheral arteries, the differences in these arteries trended much closer to significance than the values found in the carotid artery, which agrees with the conclusions of Seals et al (2008).

It may be important to consider brachial and popliteal IMT in the context of energy balance given that caloric restriction has been associated with reduced vascular remodeling in rats (Dolinsky et al, 2010). Dolinsky et al (2010) studied hypertensive rats and found that caloric restriction is associated with reduced artery wall thickness and reduced inward remodeling of artery walls. Although the exact mechanism through which remodeling is disrupted is unknown, it may be due to reduced action of smooth muscle and endothelial cells (Dolinsky et al, 2010).

One explanation for the lack of difference between the groups in the brachial and popliteal vessels is the possibility that RE may have been in a negative energy balance based on caloric expenditure and caloric intake imbalance. There is a significant between group difference in MET-min/wk, and although there is not a similar significance in caloric intake, it appears that RE has a lower caloric intake (1739.03 ± 605.37 kcal) than the other two groups (LE= 2241.24 ± 939.53 kcal and SE= 2104.98 ± 712.55 kcal). Given the high rate of turnover in endothelial cells and other vascular tissue associated with increased flow and volume rates from exercise, as well as the increased caloric need associated with exercise training, it is possible that nutrition was inadequate to meet the growth and repair needs of the vasculature. The caloric deficit may play a role in vascular remodeling, affecting the effect of physical activity on IMT in the extremities. When MET-min/wk and food frequency derived caloric intake were used as covariates, differences in IMT in the brachial and popliteal arteries were both significant (p=0.035 and p=0.038 respectively).

In addition to caloric deficit, there are other dietary factors that are related to IMT and vascular health including fiber, whole grains, fruits, berries and polyunsaturated fatty acids (Buil-Cosiales et al, 2009; Mellen et al, 2007; Ellingsen et al, 2008; Yamada et al, 1997; Hill et al, 2007). Buil-Cosiales studied the relationship between fiber intake and carotid IMT in men and women and found an inverse correlation between fiber intake and carotid IMT. Mellen et al (2007) found an inverse relationship between whole grain intake and carotid IMT, even when adjusted for energy intake, expenditure and cardiovascular disease risk factors. Hill et al (2007) observed a significant increase in flow-mediated dilation in men and women after a 12 week fish oil intervention as compared to a control group. Both Yamada et al (1997) and Djousse et al (2003) observed lower carotid IMT measurements in subjects living in fishing villages and consuming large amounts of omega-3 fatty acids than those living in farming villages and consuming measurably less, however these studies failed to account for factors such as exercise or leisure time physical activity. In the present study, intake of specific polyunsaturated fatty acids, specifically docosahexanoic acid, octadecatetranoic acid, and docosapentanoic acid, were negatively correlated with popliteal artery IMT ($r = -0.338$, -0.399, and -0.337, respectively; $p < 0.05$). Based on this data, it appears that diet, specifically energy balance and intake of the discussed nutrients, may play an important role in artery IMT and may affect the degree to which exercise can impact IMT. Therefore, energy expenditure and dietary factors should be taken into account in future research on this subject.

Previous research has provided evidence that overall vessel size may change with training (Billinger et al, 2009; Miyachi et al, 2001; Prior et al, 2003). Billinger et al

(2009) found significant increases in femoral artery diameter in the hemiparetic leg of stroke patients after 4 weeks of single leg exercises as compared to the non-exercised limb. Tronc et al (1996) provided evidence for the theory that high flow demands through arteries, such as the demand created by exercise, cause remodeling of vessels, specifically increases in vessel diameter. They found that areas of the carotid artery that were subject to high-flow through an arteriovenous shunt increased in diameter compared to the low flow region of the artery. Miyachi et al (2001) provided evidence that such arterial changes are seen in arteries supplying active muscle groups as compared to inactive muscles. They found a 16% increase in femoral cross-sectional area in a single exercising leg as compared to its non-exercising counterpart, which experienced no change in cross-sectional area.

Past research has used artery lumen diameter and total wall thickness in the analysis of IMT (Abergel et al, 1998; Moreau et al, 2002; Tanaka et al, 2002). Abergel et al (1998) reported absolute IMT, diameter and wall thickness of the carotid artery when comparing vessel difference between professional cyclists and sedentary controls. Although they found significant differences between the groups in IMT and diameter, there was no difference in total wall thickness. Moreau et al (2002) measured femoral artery IMT as well as lumen diameter in sedentary and endurance trained post-menopausal women both on and off hormone replacement therapy (HRT). While they did observe significantly lower IMT in the endurance trained women, after adjusting for lumen diameter, the difference became insignificant (Moreau et al, 2002). This suggests that other arterial changes, such as changes in lumen diameter and total artery wall thickness, may affect differences seen in IMT and future research should continue to use

IMT to lumen diameter ratios in addition to absolute IMT thickness when reporting potential changes or differences in artery IMT.

Another factor that may have contributed to the lack of significance in IMT between the groups was limited statistical power. Based on data from other studies, the original aim was to recruit and test 15 to 20 subjects in each group; instead the sample sizes were 10, 8 and 17 for SE, RE and LE, respectively. This may have negatively affected our ability to detect potentially meaningful differences between groups. For example, using equations from Lipsey (1990), an effect size of 0.934 was calculated for potential differences in the popliteal values between sedentary (IMT = 0.567) and recently active (IMT = 0.463) groups. If an effect of this effect magnitude was observed in a sample of 17-18 subjects (i.e. similar to the originally desired sample size) it is estimated that the present design would detect this difference between groups with a statistical power = 0.80 (assuming a two tailed alpha of .05; Lipsey, M.W., 1990). However with the present sample sizes, the statistical power needed to detect differences were between 0.45 and 0.50, indicating greater likelihood of a type II error.

Agreeing with previous research (Mattusch et al, 2000; Ford, 2002; Lakka et al, 2005), we found a significant difference in CRP between the exercising groups and the non-exercisers (p=0.018). However, the current study failed to find significant between group differences in IMT, suggesting that the two factors may have a limited relationship. Contradictory to our findings, previous research has found an association between increasing levels of CRP and increasing carotid artery IMT (Sitzer et al, 2002; Makita et al, 2005; Elias-Smale et al, 2007). However, Sitzer et al (2002) and Elias-Smale et al (2007) found that this relationship was lessened when other cardiovascular risk factors were accounted for. These data suggest that it is possible that inflammation may occur in the absence of significant intima-media thickening or prior to atherogenesis.

Although the results of the current study did not find any absolute difference between the exercising and non-exercising groups in terms of carotid, brachial, or popliteal artery IMT, the data indicates that a variety of other factors, including energy balance and specific dietary components may have affected the analysis. Additionally, it is possible that when IMT values are considered in relation to overall vessel wall thickness or lumen diameter that the outcome may have been different. These factors should be considered in future research.

Conclusions and Recommendations

Based on the results of this study, carotid artery IMT is not significantly different between SE, RE, and LE men. Absolute brachial and popliteal IMT are not significantly different between activity levels, but may be significant if differences in caloric expenditure and caloric intake are accounted for. Several other dietary factors may play a role in vascular remodeling and therefore affect the effect of physical activity on IMT, so further research including specific dietary measures such as caloric intake and omega-3 fatty acid intake should be completed to clarify their potential role. IMT differences between activity groups are more pronounced in peripheral arteries near active and passively active muscle groups, specifically the popliteal and brachial arteries, than in the carotid artery. Vascular anatomy, specifically artery diameter and total artery wall thickness, may differ between activity groups, thus these indices should be studied in addition to IMT in future research on the impact of exercise on IMT. CRP is significantly different between activity groups, however it is not related to differences in carotid, brachial, and popliteal IMT.

Appendix A

James Madison University
School of Kinesiology and Recreation Studies

Subject Categories and Guidelines

For the purposes of this questionnaire vigorous and moderate activity are defined as:

> **Vigorous** physical activities refer to activities that take hard physical effort and make you breathe much harder than normal.
>
> **Moderate** activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal.

Sedentary

1) Have you participated in any kind of exercise training program for more than 3 consecutive months during the last 5 years?
2) Have you participated in any kind of exercise training program for more than 2 consecutive weeks in the last year?
3) Have you participated in any kind of exercise training program at all in the last 3 months?
4) Any current participation in vigorous activity?

Recent regular aerobic exerciser

1) Have you participated in **moderate** to **vigorous** aerobic activity for an average of 120 min per week or more, spread over no less than 3 days per week during the last 6 months to 2 years?
2) Do you participate in **vigorous** activity at least 60 minutes per week?
3) Does your **moderate** and **vigorous** activity engage major muscle groups in the legs and does not engage or only passively engages major muscle groups in the arms (e.g., cycling, jogging or running)?
4) Prior to beginning participation in **moderate** to **vigorous** activity (2 or more years ago) did you meet the guidelines for the sedentary category for at least 5 consecutive years?

Long term aerobic exerciser

1) Have you participated in **moderate** to **vigorous** aerobic activity for an average of 120 min per week or more, spread over no less than 3 days per week during the last 10 years?
2) Do you participate in **vigorous** activity at least 60 minutes per week?
3) Have you been "sedentary" for more than 3 consecutive months in any of the last 10 years or for more than 4 consecutive weeks in the last year?
4) Does your **moderate** and **vigorous** activity engage major muscle groups in the legs and does not engage or only passively engages major muscle groups in the arms (e.g., cycling, jogging or running)?

Appendix B

AHA/ACSM Health/Fitness Facility Preparticipation Screening Questionnaire

Assess your health needs by marking all *true* statements.

History

You have had:

___ A heart attack
___ Heart surgery
___ Cardiac catheterization
___ Coronary angioplasty (PTCA)
___ Pacemaker/implantable cardiac defibrillator/rhythm disturbance
___ Heart valve disease
___ Heart failure
___ Heart transplantation
___ Congenital heart disease

Symptoms

___ You experience chest discomfort with exertion.
___ You experience unreasonable breathlessness.
___ You experience dizziness, fainting, blackouts.
___ You take heart medications.

If you marked any of the statements in this section, consult your physician or other appropriate healthcare provider before engaging in exercise. You may need to use a facility with a ***medically qualified staff****.*

Other health issues

___ You have diabetes
___ You have or asthma other lung disease.
___ You have burning or cramping in your lower legs when walking short distances.
___ You have musculoskeletal problems that limit your physical activity.
___ You have concerns about the safety of exercise.
___ You take prescription medication(s).
___ You are pregnant.

Cardiovascular risk factors

___ You are a man older than 45 years.
___ You are a woman older than 55 years, you have had a hysterectomy, or you are postmenopausal.
___ You smoke, or quite within the previous 6 mo.
___ Your BP is greater than 140/90.
___ You don't know your BP.
___ You take BP medication.
___ Your blood cholesterol level is >200 mg/dL.
___ You don't know your cholesterol level.
___ You have a close blood relative who had a heart attack before age 55 (father or brother) or age 65 (mother or sister).
___ You are physically inactive (i.e., you get less than 30 min. of physical activity on at least 3 days per week).
___ You are more than 20 pounds overweight.

If you marked two or more of the statements in this section, you should consult your physician or other appropriate healthcare provider before engaging in exercise. You might benefit by using a facility with a ***professionally qualified exercise staff*** *to guide your exercise program.*

___ None of the above is true.

You should be able to exercise safely without consulting your physician or other healthcare provider in a self-guided program or almost any facility that meets your exercise program needs.

Balady et al. (1998). AHA/ACSM Joint Statement: Recommendations for Cardiovascular Screening, Staffing, and Emergency Policies at Health/Fitness Facilities. *Medicine & Science in Sports & Exercise*, 30(6). (Also in: *ACSM's Guidelines for Exercise Testing and Prescription*, 7th Edition, 2005. Lippincott Williams and Wilkins http://www.lww.com)

www.acsm-msse.org/pt/pt-core/template-journal/msse/media/0698c.htm

Appendix C

James Madison University
School of Kinesiology and Recreation Studies

Physician's Consent to Maximal Exercise Testing

______________________________ is requesting physician's clearance to participate in a maximal exercise test that is a part of a study being conduct in the Kinesiology Department at James Madison University. The purpose of this study is to compare carotid, brachial and popliteal intimal-medial thickness among sedentary, recent regular aerobic exercise particpants and long term regular aerobic exercise participants between 40 and 60 years old.

______________________________ has been screened using the attached questionnaire that is recommended by the American Heart Association and the American College of Sports Medicine for participation in physical exercise (ACSM, 2010). Potential participants with two or more "cardiovascular risk factors" and/or "other heath issues" but without any history or symptoms identified in the questionnaire may be allowed to participate in the study, inclusive of the maximal exercise testing, pending physician's approval. The maximal exercise test will be conducted as follows:

> The test will be performed on a cycle ergometer to determine maximal oxygen uptake. Before the test, the researcher will explain the testing protocol to the subject. Participants will warm-up for at least five minutes at a self-selected cadence and resistance load (totaling less than 25 Watts).
>
> During the test participants will cycle at constant self-selected cadence (between 70 and 90 rpm) and the resistance load will be increased every three minutes. Participants will be fitted with a heart rate monitor, blood pressure cuff, mouthpiece and nose clip and these devices will be worn throughout the test. Heart rate will be measured every minute during the test. Blood pressure and ratings of perceived exertion will be assessed in the last minute of each stage of the test.
>
> The subject will continue the test until they request to stop, the researcher observes a plateau in the oxygen uptake or if the participant shows any of the ACSM's criteria for exercise test termination including:
>
> - Onset of moderate-to-severe angina
> - Drop in systolic blood pressure (SBP) below standing resting pressure or drop in SBP with increasing workload accompanied by signs or symptoms
> - Signs of poor perfusion, including pallor, cyanosis, or cold and clammy skin
> - Severe or unusual shortness of breath
> - Suspicion of a myocardial infarction or acute myocardial infarction
> - CNS symptoms (e.g., ataxia, vertigo, visual or gait problems, confusion)

When the subject request to stop or the researcher stops the test, the subject will cool down for at least five minutes at a low pedaling rate (less than 60 rpm) with minimal resistance. The subject's heart rate will be monitored until decreases to 110 bpm or less.

Any emergencies will be responded to by activating the University's medical emergency services.

I ________________________, have read the above request and protocol explanation and clear my patient________________________ to participate in the maximal exercise test described above .

______________________ ______________________

Signed **Date**

Appendix D

INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE
(October 2002)

Long Form: Last 7 Days, Self-Administered Format

FOR USE WITH YOUNG AND MIDDLE-AGED ADULTS (15-69 years)

The International Physical Activity Questionnaires (IPAQ) comprises a set of 4 questionnaires. Long (5 activity domains asked independently) and short (4 generic items) versions for use by either telephone or self-administered methods are available. The purpose of the questionnaires is to provide common instruments that can be used to obtain internationally comparable data on health–related physical activity.

Background on IPAQ

The development of an international measure for physical activity commenced in Geneva in 1998 and was followed by extensive reliability and validity testing undertaken across 12 countries (14 sites) during 2000. The final results suggest that these measures have acceptable measurement properties for use in many settings and in different languages, and are suitable for national population-based prevalence studies of participation in physical activity.

Using IPAQ

Use of the IPAQ instruments for monitoring and research purposes is encouraged. It is recommended that no changes be made to the order or wording of the questions as this will affect the psychometric properties of the instruments.

Translation from English and Cultural Adaptation

Translation from English is encouraged to facilitate worldwide use of IPAQ. Information on the availability of IPAQ in different languages can be obtained at www.ipaq.ki.se. If a new translation is undertaken we highly recommend using the prescribed back translation methods available on the IPAQ website. If possible please consider making your translated version of IPAQ available to others by contributing it to the IPAQ website. Further details on translation and cultural adaptation can be downloaded from the website.

Further Developments of IPAQ

International collaboration on IPAQ is on-going and an ***International Physical Activity Prevalence Study*** is in progress. For further information see the IPAQ website.

More Information

More detailed information on the IPAQ process and the research methods used in the development of IPAQ instruments is available at www.ipaq.ki.se and Booth, M.L. (2000). *Assessment of Physical Activity: An International Perspective.* Research Quarterly for Exercise and Sport, 71 (2): s114-20. Other scientific publications and presentations on the use of IPAQ are summarized on the website.

INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE

We are interested in finding out about the kinds of physical activities that people do as part of their everyday lives. The questions will ask you about the time you spent being physically active in the **last 7 days**. Please answer each question even if you do not consider yourself to be an active person. Please think about the activities you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise or sport.

Think about all the **vigorous** and **moderate** activities that you did in the **last 7 days**. **Vigorous** physical activities refer to activities that take hard physical effort and make you breathe much harder than normal. **Moderate** activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal.

PART 1: JOB-RELATED PHYSICAL ACTIVITY

The first section is about your work. This includes paid jobs, farming, volunteer work, course work, and any other unpaid work that you did outside your home. Do not include unpaid work you might do around your home, like housework, yard work, general maintenance, and caring for your family. These are asked in Part 3.

1. Do you currently have a job or do any unpaid work outside your home?

☐ **Yes**

☐ **No** → *Skip to PART 2: TRANSPORTATION*

The next questions are about all the physical activity you did in the **last 7 days** as part of your paid or unpaid work. This does not include traveling to and from work.

2. During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, digging, heavy construction, or climbing up stairs **as part of your work**? Think about only those physical activities that you did for at least 10 minutes at a time.

_____ **days per week**

☐ No vigorous job-related physical activity → ***Skip to question 4***

3. How much time did you usually spend on one of those days doing **vigorous** physical activities as part of your work?

_____ **hours per day**

_____ **minutes per day**

4. Again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate** physical activities like carrying light loads **as part of your work**? Please do not include walking.

_____ **days per week**

☐ No moderate job-related physical activity → ***Skip to question 6***

5. How much time did you usually spend on one of those days doing **moderate** physical activities as part of your work?

_____ **hours per day**

_____ **minutes per day**

6. During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time **as part of your work**? Please do not count any walking you did to travel to or from work.

_____ **days per week**

☐ No job-related walking → ***Skip to PART 2: TRANSPORTATION***

7. How much time did you usually spend on one of those days **walking** as part of your work?

_____ **hours per day**

_____ **minutes per day**

PART 2: TRANSPORTATION PHYSICAL ACTIVITY

These questions are about how you traveled from place to place, including to places like work, stores, movies, and so on.

8. During the **last 7 days**, on how many days did you **travel in a motor vehicle** like a train, bus, car, or tram?

_____ **days per week**

☐ No traveling in a motor vehicle → ***Skip to question 10***

9. How much time did you usually spend on one of those days **traveling** in a train, bus, car, tram, or other kind of motor vehicle?

_____ **hours per day**

_____ **minutes per day**

Now think only about the **bicycling** and **walking** you might have done to travel to and from work, to do errands, or to go from place to place.

10. During the **last 7 days**, on how many days did you **bicycle** for at least 10 minutes at a time to go **from place to place**?

_____ **days per week**

☐ No bicycling from place to place → ***Skip to question 12***

11. How much time did you usually spend on one of those days to **bicycle** from place to place?

_____ **hours per day**

_____ **minutes per day**

12. During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time to go **from place to place**?

_____ **days per week**

☐ No walking from place to place → ***Skip to PART 3: HOUSEWORK, HOUSE MAINTENANCE, AND CARING FOR FAMILY***

13. *How much time did you usually spend on one of those days* ***walking*** *from place to place?*

_____ **hours per day**

_____ **minutes per day**

PART 3: HOUSEWORK, HOUSE MAINTENANCE, AND CARING FOR FAMILY

This section is about some of the physical activities you might have done in the **last 7 days** in and around your home, like housework, gardening, yard work, general maintenance work, and caring for your family.

14. Think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, chopping wood, shoveling snow, or digging **in the garden or yard**?

_____ **days per week**

☐ No vigorous activity in garden or yard → ***Skip to question 16***

15. How much time did you usually spend on one of those days doing **vigorous** physical activities in the garden or yard?

_____ **hours per day**

_____ **minutes per day**

16. Again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate** activities like carrying light loads, sweeping, washing windows, and raking **in the garden or yard**?

_____ **days per week**

☐ No moderate activity in garden or yard → ***Skip to question 18***

17. How much time did you usually spend on one of those days doing **moderate** physical activities in the garden or yard?

_____ **hours per day**

_____ **minutes per day**

18. Once again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate** activities like carrying light loads, washing windows, scrubbing floors and sweeping **inside your home**?

_____ **days per week**

☐ No moderate activity inside home → ***Skip to PART 4: RECREATION, SPORT AND LEISURE-TIME PHYSICAL ACTIVITY***

19. How much time did you usually spend on one of those days doing **moderate** physical activities inside your home?

_____ **hours per day**

_____ **minutes per day**

PART 4: RECREATION, SPORT, AND LEISURE-TIME PHYSICAL ACTIVITY

This section is about all the physical activities that you did in the **last 7 days** solely for recreation, sport, exercise or leisure. Please do not include any activities you have already mentioned.

20. Not counting any walking you have already mentioned, during the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time **in your leisure time**?

_____ **days per week**

☐ No walking in leisure time → ***Skip to question 22***

21. How much time did you usually spend on one of those days **walking** in your leisure time?

_____ **hours per day**

_____ **minutes per day**

22. Think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **vigorous** physical activities like aerobics, running, fast bicycling, or fast swimming **in your leisure time**?

_____ **days per week**

☐ No vigorous activity in leisure time → ***Skip to question 24***

23. How much time did you usually spend on one of those days doing **vigorous** physical activities in your leisure time?

_____ **hours per day**

_____ **minutes per day**

24. Again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate** physical activities like bicycling at a regular pace, swimming at a regular pace, and doubles tennis **in your leisure time**?

_____ **days per week**

☐ No moderate activity in leisure time → ***Skip to PART 5: TIME SPENT SITTING***

25. How much time did you usually spend on one of those days doing **moderate** physical activities in your leisure time?

_____ **hours per day**

_____ **minutes per day**

PART 5: TIME SPENT SITTING

The last questions are about the time you spend sitting while at work, at home, while doing course work and during leisure time. This may include time spent sitting at a desk, visiting friends, reading or sitting or lying down to watch television. Do not include any time spent sitting in a motor vehicle that you have already told me about.

26. During the **last 7 days**, how much time did you usually spend **sitting** on a **weekday**?

_____ **hours per day**

_____ **minutes per day**

27. During the **last 7 days**, how much time did you usually spend **sitting** on a **weekend day**?

_____ **hours per day**

_____ **minutes per day**

This is the end of the questionnaire, thank you for participating.

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