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BODY COMPOSITION AND CAROTID ARTERY INTIMA-MEDIA
THICKNESS IN 12 TO 17-YEAR-OLD ADOLESCENTS

by

Jennifer Jane Willis

A thesis submitted to the faculty of

Brigham Young University

in partial fulfillment of the requirements for the degree of

Master of Science

Department of Exercise Sciences

Brigham Young University

August 2009

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BRIGHAM YOUNG UNIVERSITY

GRADUATE COMMITTEE APPROVAL

of a thesis submitted by

Jennifer Jane Willis

This thesis has been read by each member of the following graduate committee and by majority vote has been found to be satisfactory.

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As chair of the candidate's graduate committee, I have read the thesis of Jennifer Jane Willis in its final form and have found that (1) its format, citations, and bibliographical style are consistent and acceptable and fulfill university and department style requirements; (2) its illustrative materials including figures, tables, and charts are in place; and (3) the final manuscript is satisfactory to the graduate committee and is ready for submission to the university library.

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ABSTRACT

BODY COMPOSITION AND CAROTID ARTERY INTIMA-MEDIA THICKNESS IN 12 TO 17-YEAR-OLD ADOLESCENTS

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Master of Science

Background and Purpose—There is controversy in the literature regarding the relationship between intima-media thickness (IMT) and body composition among adolescents. This study investigated the relationship between body fat percentage and IMT, while controlling for height, weight, age, blood pressure, cholesterol, glucose, triglycerides and VO₂max in 12 to 17-year-old children.

Methods—111 children (mean age = 14.33 years) participated in this study. Body fat percentage was assessed using dual energy x-ray absorptiometry (DXA). A B-mode, high-resolution ultrasonograph was used to measure the IMT of the right and left common carotid arteries (CCA). Fasting blood tests were performed to obtain blood lipid and glucose profiles. Blood pressure was measured using an automatic blood pressure cuff.

Results—Data were divided into body fat tertiles to compare differences between the upper and lower tertile. Contrary to what might be expected, the mean IMT of the group with the lowest body fat percent was 0.516 mm and the mean IMT for the upper tertile of

body fat percent was 0.483 mm ($F(2,103) = 5.883, p = 0.004$). Post hoc analysis indicated that the two leanest groups had significantly thicker IMT than the group with the highest percent body fat ($p = 0.005$ and $p = 0.027$, respectively). The two leanest groups were not significantly different from each other. When controlling for gender, no significant relationship existed between CCA-IMT and body fat percentage ($F(2,103) = 2.267, p = 0.109$).

Conclusions—This study found that there were significant differences in IMT between body fat percentage and CCA-IMT in children and adolescents 12 to 17-years of age. This study did indicate that as body fat increases, risk factors such as cholesterol and triglycerides also increase. Overall, the direct relationship between CCA-IMT and body fat percentage is poorly understood in children and adolescents. Further research is necessary to determine a standardized protocol for assessing atherosclerotic risk in adolescents.

Key Words: Intima-media thickness, body fat, carotid arteries, adolescents

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THICKNESS

BODY COMPOSTION AND CAROTID ARTERY INTIMA-MEDIA THICKNESS IN
12 TO 17-YEAR-OLD ADOLESCENTS

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Abstract

Background and Purpose—There is controversy in the literature regarding the relationship between intima-media thickness (IMT) and body composition among adolescents. This study investigated the relationship between body fat percentage and IMT, while controlling for height, weight, age, blood pressure, cholesterol, glucose, triglycerides and VO_2 max in 12 to 17-year-old children.

Methods—111 children (mean age = 14.33 years) participated in this study. Body fat percentage was assessed using dual energy x-ray absorptiometry (DXA). A B-mode, high-resolution ultrasonograph was used to measure the IMT of the right and left common carotid arteries (CCA). Fasting blood tests were performed to obtain blood lipid and glucose profiles. Blood pressure was measured using an automatic blood pressure cuff.

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Conclusions—This study found that there were significant differences in IMT between body fat percentage and CCA-IMT in children and adolescents 12 to 17-years of age. This study did indicate that as body fat increases, risk factors such as cholesterol and triglycerides also increase. Overall, the direct relationship between CCA-IMT and body fat percentage is poorly understood in children and adolescents. Further research is necessary to determine a standardized protocol for assessing atherosclerotic risk in adolescents.

Key Words: Intima-media thickness, body fat, carotid arteries, adolescents

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Introduction

The relationship between intima-media thickness (IMT) and body composition in children is a focus of ongoing debate. There is a need for further research on the relationship between body fat percentage and carotid atherosclerosis.¹ It is not entirely clear whether obesity alone or obesity and other risk factors are related to IMT in children. It is well known that obesity is linked with increased risk for coronary heart disease (CHD) and that childhood obesity leads to adulthood obesity.^{2,3} The sonographic assessment of the IMT of the common carotid artery (CCA) is a common method of measuring atherosclerotic burden and changes over time.⁴ Using high resolution B-mode ultrasound, atherosclerosis can be detected early by measuring thickness of the arterial wall.⁵

The IMT of the CCA is used as a measurement of coronary atherosclerosis primarily in middle-aged and elderly populations. There is limited evidence in children and adolescents regarding the relationship between IMT and body composition, with some results indicating early initial stages of atherosclerosis being associated with body composition.⁴ However, the evidence that does exist is poorly understood, and other studies do not support such a relationship.^{6,7}

No firm conclusion has been reached as to whether or not CCA-IMT increases with increasing body fat percentages in children. Reinehr et al.⁴ found that obese children had a significantly ($p < 0.001$) thicker intima media (median, 0.6 mm) than a non-obese control group (0.4 mm). They also found that IMT was significantly correlated to the percentage of body fat ($r = 0.29$, $p = 0.001$).⁴ A study completed by

Tounian et al.⁶ did not completely support the Reinehr study. In the cross sectional study by Tounian et al. severely obese children (>95th percentile) had increased arterial stiffness compared to healthy-weight children, but there was no significant difference in carotid IMT between the two groups.⁶

The relationship between IMT and body composition in children remains unclear, which leads to the necessity of further study. The purpose of the present study was to investigate the relationship between body composition and IMT in 111 boys and girls between the ages of 12 and 17 years.

Methods

Study Population

The 111 boys and girls (n = 53 girls, n = 58 boys) that participated in the study were recruited from several cities in Utah county, Utah. The children were between the ages of 12 and 17 years. Children were primarily notified by flyers sent to faculty and staff at Brigham Young University (BYU), Utah Valley University (UVU) and local middle schools and high schools.

Prior to recruiting participants and collecting data, the methods of this study and the informed consent process was reviewed and approved by the Institutional Review Board (IRB) for the use of human subjects at BYU. Prior to participating in the study, each participant and his/her parent(s) were informed of the procedures of the study and all participants signed an assent form and parents signed a parental permission form.

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Height and Weight

Height (cm) was measured and recorded for each participant using a calibrated wall scale to the nearest one-half inch. Weight was measured and recorded for each participant using a digital scale (Ohaus Model CD-33, Ohaus Corporation, Pine Brook NJ, USA) to the nearest one-tenth of a pound. Body mass index (BMI) was calculated from measured height and weight values.

Cardiorespiratory Fitness

Cardiorespiratory fitness ($VO_2\text{max}$) was measured during a maximal graded exercise treadmill test (GXT). Participants completed a GXT on a motor-driven treadmill (Model TMX425C, Full Vision, Inc., Newton, KS). Each participant wore a mouthpiece and a nose clip in order to measure their metabolic and ventilatory responses during the test using a calibrated Truemax 2400 metabolic cart (Consentious Technologies, Sandy, UT). A radiotelemetry heart-rate (HR) monitor (Polar Electro OY, Hong Kong) was used to measure HR. A Borg 15-point scale was used to monitor rating of perceived exertion (RPE).⁸

Participants completed a submaximal exercise treadmill test prior to the maximal GXT. The submaximal exercise test consisted of three stages; walking at 3.0-4.0 mph, jogging at 4.1 mph-6.0 mph, and running at 4.1-6.0mph. Beginning with the walking stage, participants progressed through each stage, as needed until he/she reached a steady-state heart rate of at least 70% of his or her age predicted maximum heart rate ($220-\text{age}$). Subjects then completed a maximal GXT^{9,10} following a minimum of 10 minutes of rest. The treadmill speed remained constant during the test at the speed that

elicited 70% of age-predicted maximal heart rate, while the grade was increased 1.5% each minute until the subject could no longer continue. The effort of each subject was accepted as maximal if physical exhaustion was apparent and at least two of the following conditions were met: (a) maximal RER > 1.0, (b) no further increase in HR despite an increase in workload, or (c) a maximal HR that was at least 85% of age-predicted maximal HR.

Resting Blood Pressure

Resting blood pressure was measured with an automatic blood pressure monitor (Omron Model HEM-790IT, Omron Healthcare, Inc., Bannockburn, Illinois, USA) on the left arm, in the seated position following a minimum of five minutes of rest. The average of three systolic and diastolic blood pressure values was recorded.

Blood Lipid Profile

Blood was drawn at the university's student health center to determine blood levels of triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC) and glucose (GLU). Participants were instructed to fast for 8-12 hours prior to having their blood drawn. Blood samples were collected by venipuncture. All analyses were conducted using accepted laboratory assay protocols. VLDL and LDL were calculated using the following formulas: $VLDL = TG/5$ and $LDL = CHO - HDL - VLDL$.

Body Composition

Body composition was assessed using dual-energy x-ray absorptiometry (DXA). All DXA scans were performed by a Utah state certified technician using a Hologic

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QDR4500 scanner (Hologic Inc., Bedford, MA) and software version 11.2 with supplemental pediatric software. Manufacturer recommended operating procedures for whole-body scans were followed. Each scan was completed in approximately seven minutes. Body composition was reported as the percentage of body weight that was fat.

High-Resolution Carotid Ultrasound

The methodology for the SonoCalc automated software analysis ultrasound system used in this study was described and validated by Fritz et al.¹¹ All images were taken from the right and left common carotid artery using a Sonosite Titan Ultrasound system (Sonosite Inc., Bothell, WA). The Sonosite Titan system is an M-mode, high-resolution ultrasonograph, equipped with a 5-MHz traducer. Images from an anterior, direct, and posterior view were captured and analyzed for thickness of the arterial wall. Each image of the right and left common carotid arteries was captured by the same technician. All images were measured twice to ensure intra-rater reliability. An intraclass correlation was performed to ensure accuracy of the measurements. Intra-rater reliability was high ($r = 0.90$, $p < 0.001$).

Images were captured at a point 1 cm proximal to the common carotid bifurcation. A trained researcher analyzed all images of the CCA using the SonoCalc software system to determine the average IMT of the captured images. Measurements were taken only from the far arterial wall due to the increased reliability.¹² The average carotid IMT was used in data analysis.

Statistical Analysis

Statistical analysis was performed using SPSS, version 11.5.0 (SPSS Inc., Chicago, IL). Analysis of Variance (ANOVA) was used to determine differences in the dependent variable (IMT) by levels of body fat percentage. Analyses for differences in the dependent variable were conducted independent of potential confounding factors and also with control for potential confounding factors. For all statistical procedures, $p \leq 0.05$ was used to determine significance. Additionally, Pearson correlation coefficients were used to describe relationships between variables of interest.

Results

Table 1 provides descriptive characteristics for the entire sample of subjects. The descriptive table also shows that there were significant differences between boys and girls for IMT, height, BMI, percent body fat, glucose, VO_2 (l/min), and VO_2 (ml/kg/min).

IMT and Body Composition

Pearson Correlation indicated a significant inverse relationship between IMT and BF% ($r = -0.294$, $p = 0.002$). ANOVA for IMT x BF% tertiles without control for any potential confounding factors confirmed the inverse findings of the correlation. When subjects were grouped by tertiles according to natural cut-points, a significant main effect was noted ($F(2,103) = 5.88$, $p = 0.004$). The mean IMT for the leanest, middle and fattest BF% tertiles were 0.516 mm, 0.510 mm, and 0.483 mm, respectively (Table 2). Tukey post-hoc analysis identified significant differences between the leanest tertile and the fattest tertile groups ($p = .005$) and the middle tertile compared to the fattest tertile ($p = .027$). The leanest tertile and middle tertile were not significantly different from each

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other. When controlling for gender, the trend in the mean IMT decreasing from leanest to fattest still existed (0.513 mm, 0.507 mm, and 0.481 mm, respectively); however, the differences were not significant ($F(2,100) 2.27, p = 0.109$).

Fitness, Body Composition, and IMT

Given the results of the ANOVA for IMT and BF% additional analyses were conducted. Bivariate correlation for fitness (VO_2 max) was significantly inversely correlated to BF% ($r = -0.863, p < 0.001$). Using the same tertiles for BF% as previously described and with fitness as the dependent variable, ANOVA indicated a significant main effect for fitness x BF% tertiles ($F(2,87) 59.46, p < 0.001$). Tukey post-hoc analysis showed that all three BF% groups differed significantly from each other ($p < 0.001$ for all three comparisons). Further analysis showed that IMT and fitness were positively significantly correlated ($r = 0.235, p = 0.03$).

Other Findings

A positive correlation was noted between body fat percentage and total cholesterol ($r = 0.321, p = 0.01$), LDL-cholesterol ($r = 0.288, p < 0.01$), VLDL-cholesterol ($r = 0.308, p < 0.01$) and triglycerides ($r = 0.310, p < 0.01$).

Discussion

The primary purpose of this study was to determine the relationship between body fat percentage and CCA-IMT. This study was a cross sectional analysis of 111 boys and girls ranging between 12 and 17 years in age. A significant inverse relationship existed between IMT and BF% ($r = -0.294, p = 0.002$). These results were unexpected; however, there are some logical explanations and previous research that support the findings.

One reason for the inverse relationship was due to differences between boys and girls BF%. Boys had a mean BF% of 15.5% while the girls had a mean BF% of 27.7% ($p < 0.001$). Additionally, there was also a difference in IMT between boys and girls with an average IMT of 0.512 mm for boys and 0.489 mm for girls ($p = 0.008$). The girls in this study had the thinnest IMT. Yet, they were also significantly fatter than the boys. Without controlling for gender, the significance and trend for decreasing thickness in IMT with increasing BF% was likely due to the influence of gender. When gender was controlled for, the inverse relationship still existed; however, it was not significant.

The differences in IMT for varying levels of BF% can possibly be further explained by the fitness levels of the boys and girls. A significant inverse correlation existed between fitness and BF%, indicating that more fit children have a lower body fat percentage. The boys were the leanest group and the girls were the fattest group. Additionally, the boys had a much higher fitness level than the girls ($p < 0.001$). It was also noted that as fitness level increased, IMT increased. Although evidence is not in complete agreement on this topic, studies in both humans and in rats indicate that as exercise increases arterial wall thickness also increases.^{13,14,15} The corresponding increase in IMT with increasing levels of fitness could be due to vascular muscle hypertrophy resulting from regular exercise or activity. Increases in left ventricular wall thickness as a result of aerobic training have been reported.¹⁶ During activity, blood flow and pressure increase which increased stress on the arterial wall.¹³ The vascular hypertrophy that is experienced with exercise and activity may correspond to a natural structural adaptation occurring in response to hemodynamic stress during exercise.¹³

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It is not likely that there is some amount of hypertrophy of the smooth muscle in the artery wall in response to the increase in systolic blood pressure that occurs during exercise. Further studies are needed to determine the appropriate approach to distinguish between pathological and physiological changes in IMT, as it cannot currently be determined ultrasonographically.¹³ While this study found a strong inverse correlation between IMT and BF%, other studies have reported a significant positive correlation between CCA-IMT and body fat percentage.⁴ Currently BF% and fitness as it relates to CCA-IMT appear to be topics of ongoing debate.

One reason for the discrepancy in the literature on CCA-IMT and BF% may be due to differences in measurement techniques. It has been established that when using ultrasound, only the far arterial wall measurement is a reliable measurement for determining the IMT thickness, yet some studies have utilized the combined measurement of both the near and far wall.¹⁷ It has also been established that “the near wall is unreliable even when it is well visualized.”¹² While some studies have used a measurement of the far wall only, others have combined the measurements of both the near and far walls or used the mean of the two measurements.^{18,19} Clearly, there remains controversy over the measurement technique.

Another explanation for the results of this study may be the slow progressing nature of atherosclerosis and obesity. Plaque buildup within the artery wall occurs over time as does increasing body fat percentage. Many studies in older populations have shown a substantially thicker IMT when compared to children. Given that the present study was conducted on a relatively narrow age range of children and adolescents, it may simply be that

the effects of excess BF% have not had time to affect the IMT significantly. Even though it was not found that IMT increases with increasing BF%, fatness was related to other potential health risks. As BF% increased, total cholesterol, LDL-cholesterol, VLDL-cholesterol and triglycerides also increased.

Conclusion

This study found a significant inverse relationship between body fat percentage and CCA-IMT in adolescents between 12-17 years of age. Additionally, it was noted that gender and fitness may have a confounding influence on CCA-IMT. There is some evidence in the literature that regular exercise or physical activity training may increase CCA-IMT. In the present study, boys had increased IMT, lower BF%, and higher fitness than the girls. Some, but not all research suggests a positive correlation between BF% and CCA-IMT does exist. More research is needed to clearly understand the relationship between the development of CCA-IMT in children and BF%. A standardization of CCA-IMT testing protocols and image analysis is also necessary. Overall, this study adds to the body of evidence that early intervention in children with increased BF% is warranted.

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Table 1. Descriptive Statistics with Differences for Boys and Girls

	All Subjects		Boys		Girls		F	P
	N*	Mean (SD)	N*	Mean (SD)	N*	Mean (SD)		
IMT (mm)	106	0.501 (.046)	54	0.512 (.045)	52	0.489 (.044)	7.22	.008
Age (y)	111	14.3 (1.7)	58	14.1 (1.7)	53	14.6 (1.6)	2.68	.104
Height (in)	111	64.6 (4.4)	58	65.7 (5.1)	53	63.3 (3.1)	8.83	.004
Weight (lbs)	111	126.7 (28.7)	58	126.1 (31.5)	53	127.4 (25.6)	0.06	.813
BMI	111	21.3 (3.9)	58	20.4 (3.7)	53	22.3 (3.8)	7.38	.008
Body Fat – DXA (%)	111	21.1 (8.6)	58	15.5 (6.6)	53	27.0 (6.1)	91.17	<.001
Cholesterol (mg/dl)	81	145.9 (23.8)	46	142.5 (24.7)	35	150.3 (22.1)	2.19	.142
LDL (mg/dl)	81	83.9 (20.1)	46	81.4 (21.2)	35	87.2 (18.1)	1.68	.199
HDL (mg-dl)	81	45.8 (8.9)	46	45.5 (8.8)	35	46.2 (9.1)	0.14	.712
VLDL (mg/dl)	81	16.2 (7.6)	46	15.7 (6.2)	35	17.1 (9.1)	0.60	.441
Triglycerides (mg/dl)	81	81.1 (37.5)	46	78.2 (30.4)	35	84.9 (45.5)	0.64	.427
Glucose (mg/dl)	81	83.9 (7.4)	46	85.9 (6.9)	35	81.4 (7.3)	7.88	.006
Systolic BP (mm Hg)	109	101.2 (12.5)	57	102.2 (12.5)	52	100.1 (12.6)	0.90	.345
Diastolic BP (mm Hg)	109	63.6 (8.5)	57	62.7 (7.4)	52	64.6 (9.5)	1.33	.252
VO ₂ (l/min)	90	2.81 (.75)	51	3.0 (.84)	39	2.5 (.49)	11.23	.001
VO ₂ Max (ml/kg/min)	90	49.5 (9.0)	51	54.1 (8.2)	39	43.7 (6.3)	41.55	<.001

*N varies for certain descriptive measures because all participants did not have complete data

Table 2. Multiple Regression Analysis with CCA-IMT and Body Fat

	Body Fat % Groups			F	P
	Low	Moderate	High		
	Mean (SD)	Mean (SD)	Mean (SD)		
IMT	.513 (.051)	.507 (.041)	.481 (.039)	5.12	.008
Variable Controlled					
Gender	.506	.509	.486	2.27	.109
Age (y)	.513	.508	.481	5.57	.005
Height (in)	.513	.508	.482	4.55	.013
Weight (lbs)	.513	.507	.482	4.76	.011
BMI	.513	.507	.482	3.70	.028
Cholesterol (mg/dl)	.518	.507	.480	4.64	.013
LDL (mg/dl)	.520	.506	.480	5.00	.009
HDL (mg/dl)	.513	.512	.483	3.53	.034
VLDL (mg/dl)	.514	.512	.482	3.65	.031
Triglycerides (mg/dl)	.514	.512	.482	3.68	.030
Glucose (mg/dl)	.513	.511	.484	3.12	.050
SBP (mm Hg)	.512	.507	.481	4.67	.012
DBP (mm Hg)	.512	.507	.481	4.71	.011
VO ₂ Max (ml/kg/min)	.504	.507	.495	0.36	.699
All of the Above	.489	.525	.501	2.54	.089

Means for control variables are shown as adjusted means without standard deviation

Appendix A

Prospectus

Chapter 1

Introduction

The prevalence of overweight and obesity among U.S. children has increased dramatically over the past few decades and there is no current indication that the prevalence of overweight and obesity among children will decrease. Of concern is that in a review of literature by Serdula et al. they found that, “about a third of obese children were obese as adults, and about half of school-age children were obese as adults.”¹

Overweight and obesity during childhood increases one’s risk of cardiovascular disease as an adult. Cardiovascular risk factors are identifiable in childhood and are predictive of adult cardiovascular risk. Identifying risk factors early in life and changing detrimental lifestyle habits may limit the progression of carotid artery disease. Additionally, exposure to risk factors in childhood may have long-term consequences on vascular function.²

Observations by Raitakari et al. show that childhood risk factors predict the occurrence of carotid atherosclerosis in adulthood.³ One method of determining the relationship between carotid artery disease and body composition is through carotid artery ultrasound screening. Although some research has been done in this area, there are discrepancies in the literature regarding whether or not obese children have significantly increased carotid tunica intima-media thickness (IMT) and stiffness compared to healthy control children.

Carotid artery disease results when the carotid arteries develop plaque, causing increased stiffness of the arterial wall and narrowing of the carotid lumen. The plaque is composed of cholesterol, calcium, and fibrous tissue. Carotid artery disease is characterized by a reduction in blood flow through the carotid arteries.

The risk factors for carotid artery disease are similar to those of coronary artery disease, which include high levels of low-density lipoprotein cholesterol (LDL-C) and triglycerides in the blood, hypertension, diabetes, smoking, family history of coronary artery disease, obesity, and physical inactivity.

Determining the relationship between body composition and other risk factors for carotid artery disease and carotid artery thickness in children will help increase our understanding of vascular health in children. A greater understanding of the relationship between body composition and carotid artery disease in children will be of value in developing appropriate interventions that can be implemented in the public schools and community-based fitness and recreation centers.

Statement of the Problem

The prevalence of overweight and obesity in children is increasing, resulting in an increased prevalence of obesity-related diseases in childhood and increased risk of obesity-related diseases in adulthood. The relationship between body composition and the carotid IMT in adolescents is unclear. Therefore, the purpose of this study is to evaluate the relationship between carotid IMT thickness and body composition in adolescents. A secondary purpose of this study is to evaluate the influence of other potential risk factors on the carotid IMT in adolescents.

Research Hypotheses

In adolescents 12-17 years of age, there is a strong positive linear correlation between body fat percentage and carotid IMT after controlling for height, weight, blood pressure, blood lipids, and cardiorespiratory fitness (VO₂max).

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Variance in carotid IMT between children can be accounted for by differences in height, weight, BMI, resting blood pressure, fasting blood lipids, and cardiorespiratory fitness. Thus, the carotid IMT in children and adolescents 12-17 years of age can be predicted using a regression equation developed from these variables.

Null Hypotheses

In adolescents 12-17 years of age, body fat percentage is unrelated to carotid IMT after controlling for height, weight, blood pressure, blood lipids, and VO₂max.

Variance in carotid IMT between adolescents cannot be accounted for by differences in height, weight, BMI, resting blood pressure, fasting blood lipids, and VO₂max, and the carotid IMT in adolescents 12-17 years of age cannot accurately be predicted using a regression equation developed from these variables.

Definitions of Terms

Body composition - A combination of fat mass and lean mass used to describe the composition of the human body.

Body mass index (BMI) - A commonly used indicator of adiposity in children, adolescents, and adults. Calculated by dividing weight (kg) by height (m²).

Dual-energy x-ray absorptiometry (DXA) - A method of assessing bone mineral content and bone mineral density from a two x-ray energy system. DXA is also a criterion method of assessing body composition.

Intima-media thickness (IMT) - Is also referred to as intimal medial thickness and is a measurement of the thickness of artery walls. It is measured primarily by ultrasound and is used to detect atherosclerotic disease.

Overweight - A body weight that is above the normal weight category. In children, a BMI that is at or above the 85th percentile for his/her age and gender is at risk of overweight.

Obesity - Individuals with a body weight that is much greater than what is defined as healthy. Adults with a BMI ≥ 30 are considered obese. Children are categorized as obese when they have a BMI $\geq 95^{\text{th}}$ percentile for their height and weight.

Percent body fat - The percentage of body weight that is fat.

Assumptions

The following assumptions apply to this study:

Participants have fasted for 12 hours prior to having blood drawn and fasting blood lipid profiles measured.

Participants have refrained from eating and exercising for 3-4 hours prior to having their weight and body composition measured.

Participants who participate in the studies that assess body composition and cardiorespiratory fitness will comply with all pretest instructions.

Delimitations

Participants in this study will be boys and girls between 12 and 17 years of age.

Limitations

Compliance in obtaining blood lipid profiles for young children may pose a challenge.

Dietary intake will be assessed using self-reported responses to a food frequency questionnaire.

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Most of the participants in the study will be children of faculty at Brigham Young University residing in Utah County, and may therefore not be representative of the entire population.

Chapter 2

Review of Literature

Childhood Obesity

The prevalence of overweight and obesity is an extremely important health concern in the United States. Obesity rates have reached epidemic proportions. The prevalence of overweight and obesity in children is significant because both are risk factors for cardiovascular and metabolic disease. Overweight and obesity has been identified by Healthy People 2010 as 1 of the 10 leading health indicators.² Since 1970, the increased prevalence of overweight among children between the ages of 2 and 5 years has doubled and has tripled among children and adolescents between the ages of 6 and 19 years.⁴ Overall, the number of children and adolescents now considered to be overweight exceeds 9 million, which represents approximately 17% of children and adolescents.⁴ Based on current data and trends, it is projected that, “the current epidemic of adolescent overweight will substantially increase future rates of adult coronary heart disease (CHD) unless other changes intervene. Significant morbidity and mortality are projected to begin in young adulthood, resulting in more than 100,000 excess cases of CHD by 2035, even with the most modest projection of future obesity.”⁴

Children are often categorized by age and gender for health purposes based on the U.S. children cutpoints which are defined as follows: normal weight (BMI percentile $>5^{\text{th}}$ and $<85^{\text{th}}$); at risk for overweight (BMI percentile between the 85^{th} and 95^{th}); and overweight (BMI percentile $\geq 95^{\text{th}}$ percentile).⁵ The Institute of Medicine and others also classify children with BMI $\geq 95^{\text{th}}$ percentile as obese.”⁵ Children classified as overweight

often suffer from immediate adverse health effects.⁴ Overweight teenagers often suffer from elevated BMI in young adulthood. It is estimated that 80% of overweight adolescents become obese adults.⁴ Additionally, childhood obesity is a significant risk factor for adult morbidity and mortality.⁶

Over-consumption of calories and minimal physical activity are the main culprits for childhood obesity.⁷ Physical inactivity is a major risk factor for obesity and elevated carotid IMT which culminates in premature atherosclerotic disease.⁸ “Atherosclerosis has its roots in childhood.”⁹ It then progresses through young adulthood to cause CHD later in life.”¹⁰

The financial burden associated with childhood overweight and obesity is unprecedented as well. Federal officials estimated the direct and indirect costs of the overweight and obesity epidemic to be approximately \$117 billion in 2000.⁶ Identifying risk factors early in life and making positive lifestyle changes may limit the progression of cardiovascular disease and minimize financial burden associated with disease stemming from obesity.

Carotid Ultrasound Screening

Carotid artery disease is a form of cardiovascular disease that can easily be measured. Risk factors for carotid artery disease include high levels of serum low-density lipoprotein cholesterol (LDL-C) and triglycerides, high blood pressure, diabetes, smoking, family history of coronary artery disease, obesity and physical inactivity. The relationship between the various risk factors and carotid artery disease can be investigated using a carotid artery ultrasound screening.

The measurement of the IMT of the common carotid artery (CCA) is a feasible, reliable, valid and cost-effective method of measuring atherosclerotic changes.¹¹ By utilizing B-mode ultrasound screening, the carotid tunica IMT and stiffness can be determined. The medial layer of the CCA comprises the majority of the thickness of the artery.¹²

“An early sign of atherosclerosis is hypertrophy of the arterial wall. Increased IMT is a noninvasive marker of arterial wall alteration, which can easily be assessed in the carotid arteries by high-resolution B-mode ultrasound.”¹³ In addition, carotid arterial wall IMT is predictive of CAD events.¹⁴ Increased stiffness and thickness of the CCA wall are shown to be significant predictors of cardiovascular complications mainly for myocardial infarction and for stroke.¹² Measurements of the CCA-IMT, when compared to measurements such as the bifurcation, are easier to obtain and is more reliable.³ Additionally, the ability of IMT measurements to predict future cardiovascular events slightly increases when data from all three segments, rather than from only one site are recorded.³

Carotid IMT Studies

“Intima-medial thickening in obese children is a focus of ongoing debate.”⁸ One study of obese children reported no significant differences in carotid IMT when compared with control subjects.¹⁵ Many other studies have demonstrated a correlation between increased carotid IMT and obesity in children.⁸ Several studies have been conducted regarding IMT as it correlates to health and fitness. These areas of research include carotid IMT stiffness and thickness as it correlates to body composition and other

risk factors, the correlation between number of risk factors and IMT thickness, and risk factors measured in childhood predicting IMT thickness in adulthood in relation to disease risk. While some studies are in agreement on these relationships others clearly have conflicting evidence which leads to the necessity of further study and investigation. The following studies outline the array of studies on these topics.

IMT and body composition. Reinehr et al. found that obese children had a significantly ($p < 0.001$) thicker intima media (median, 0.6mm) as compared with the control group (0.4 mm). They also found that IMT was significantly correlated to the percentage of body fat ($r = 0.29, p = 0.001$).¹¹ Iannuzzi et al. also concluded that obese children have significantly increased carotid IMT and stiffness compared with healthy control children.¹⁶ “The increased vascular IMT and stiffness in obese children compared with healthy control subjects suggests that obesity in children represents a powerful determinant of early manifestations of atherosclerosis and affects structural mechanical properties of major vessels.”¹⁶

A study completed by Tounian et al. provided contradictory information. In their cross sectional study, severely obese children (>95th percentile) had increased arterial stiffness compared to healthy-weight children, but there was no significant difference in carotid IMT between the two groups.¹⁵ The relationship between IMT and either BMI or body composition in children remains unclear.

Childhood risk factors and adult IMT. In the Bogalusa Heart Study, measurements of traditional risk factors since childhood were compared with measurements of IMT in a cohort of 486 adults. “Childhood LDL-C level, BMI, and

systolic blood pressure were correlated with carotid IMT in young adults, with LDL-C having the highest correlation. In adulthood, systolic blood pressure, LDL-C, BMI, HDL-C (inverse association) and triglyceride levels were all correlated with carotid IMT, systolic pressure and LDL-C levels showing the highest correlations.”¹⁷ In addition, the Muscatine cohort, “examined over the age range of 8 to 42 years, childhood risk factors, including total cholesterol for both sexes and BMI only for women, predicted carotid IMT.”¹⁸ They also found that carotid IMT was positively associated with levels of total serum cholesterol and BMI measured in childhood.¹⁸ Results from the Young Finns Study reaffirm the link between risk factor exposures (including LDL-C, BMI, cigarette smoking, and systolic blood pressure [SBP]) in 12 to 18-year-old adolescents and preclinical atherosclerosis in adulthood.³ Results from this population based prospective cohort study of 2,229 young adults 24 to 39 years of age are noteworthy because risk factors present in adolescence predicted adult common carotid IMT independently of contemporaneous risk factors.³

Number of risk factors and IMT. In the Atherosclerosis Risk Factors in Male-Youngsters (ARMY) study, “risk conditions were defined as smoking, low to moderate levels of HDL cholesterol, moderate to high diastolic blood pressure, high antimycobacterial HSP60 antibodies, and/or high antihuman HSP-stimulation index.” “The prevalence of high IMT substantially increased from 0 to 60% when the number of risk conditions in a single individual increased from 0 to 4 ($p < 0.001$ for linear trend).”¹⁹

Reinehr et al. concluded, “increasing IMT was significantly associated with increasing degree of overweight, SBP and DBP, and glucose and hsCRP concentrations,

whereas age, TGs, and LDL-C and HDL-C concentrations did not significantly differ between children with different IMT.”¹¹ “This is the first study in obese children concerning the changes of IMT and its relationship to the cardiovascular risk factors hypertension, dyslipidemia, impaired glucose metabolism, and chronic inflammation. IMT in obese children was significantly increased as compared with nonobese children of similar age, sex and pubertal stage indicating that arterial abnormalities are evident in obese children.¹¹

Confounding Variables

While the majority of evidence indicates that as BMI and body fat increase, IMT increases, there are many confounding lifestyle variables that have a major influence on the IMT.

“It is unclear if obesity per se or the occurrence of obesity with cardiovascular risk factors determines IMT.”¹¹ In a study completed by Iannuzzi et al., “obese children had significantly higher blood pressure and plasma concentrations of triglycerides, cholesterol, glucose, insulin, HOMA, and C-reactive protein than control subjects. Carotid thickness and stiffness were significantly different between obese and nonobese children and in both boys and girls.”¹⁶

The IMT of the CCA is also significantly influenced by age. For younger age groups (20 to 30 years) mean IMT values of 0.5 mm have been reported, while IMT values of 0.9 mm have been found for older subjects (60 to 70 years).¹³ In the National Institute for Longevity Sciences-Longitudinal Study of Aging the carotid IMT increased significantly ($p < 0.01$) with age in both genders. The mean carotid IMT of 0.61 ± 0.15

mm for men was significantly greater ($p < 0.01$) than the mean IMT in women (0.58 ± 0.14 mm).²⁰ However, this relationship does not hold true for those under 18 years of age. A major finding from the IMT study using the Stanislas cohort was, “the IMT did not increase and did not differ according to sex in children up to 18 years of age.” They concluded that sex related differences in the carotid IMT are apparent in adults 18 years of age and older.²¹

Preventative and Intervention Measures

Children with multiple risk factors are at increased risk of atherosclerosis in adulthood. Obesity beginning even in childhood should be considered a disease with vascular repercussions. Childhood and adolescence is a crucial time in which to intervene and prevent the development of overweight and obesity. During this transitional period of life, adult patterns of health and behavior are established. There are more potential interventions for children than are available for adults. Principally, the school environment is one in which children are influenced by food and physical activity.²²

The Cardiovascular Risk in Young Finns Study concluded, “children and adolescents with several risk factors are at increased risk of developing atherosclerosis in adulthood. Risk factors such as obesity, dyslipidemia, and elevated blood pressure are metabolically linked and reductions in these factors could be potentially achieved in children with lifestyle modifications such as inducing changes in diet, increasing levels of physical activity, and controlling obesity.”²³

Markus et al. concluded that a 5kg/m² reduction in BMI resulted in a 0.065 mm/year decrease in annual IMT progression. In addition, they estimated that reducing dietary cholesterol intake by 100 mg/day and quitting a 10 cigarettes/day habit, decreased IMT progression by 0.13 mm/year.¹⁴

There are many potential intervention strategies for combating childhood obesity. Several recommendations have been cited in the Journal of the American Medical Association (JAMA). Such strategies include “(1) assessing dietary patterns and lifestyle issues, environmental and social supports and barriers, and the patient’s self-efficacy and readiness to change; (2) following a staged approach to weight management with diet and physical activity, family counseling and regular follow-up aimed at keeping child and adolescent BMI within a healthy range; and (3) educating families about energy-dense foods and sweetened beverages, prescribing at least 60 minutes of moderate physical activity a day for all family members, and limiting child and adolescent daily screen time to less than two hours a day.”⁶

Increasing physical activity makes a large difference in IMT. Meyer et al. measured IMT at baseline and after six months of involvement in an exercise program which included exercise for one hour, three times per week.⁸ They concluded that a 6-month program of enhanced physical exercise improves IMT. “Significant improvements were observed in the exercise group for IMT (0.44 ± 0.08 , $p = 0.012$, -6.3%). This improvement correlated with reduced cardiovascular risk factors such as BMI standard deviation scores, body fat mass, waist/hip ratio, ambulatory systolic blood

pressure, fasting insulin, triglycerides, low density lipoprotein ratio and low degree inflammation.”⁸

The increased benefit of diet and exercise in 82 overweight children (mean BMI of $25 \pm 3 \text{ kg/m}^2$) was recognized by Woo et al.²³ The children were evaluated before and after an intervention program involving diet-only or diet-with regular exercise. Woo et al. reported, “the vascular dysfunction associated with obesity in children is partially reversible even by a short-term program of dietary modification. The addition of an individualized exercise training program for children enhanced the beneficial arterial effects, which could be sustained when training for 1 year.”²³ Overall, IMT decreases as weight decreases in obese children.¹¹

Chapter 3

Methods

Participants

Subjects for this study will include boys and girls between 12 and 17 years of age. Each age will be equally represented by 15 boys and 15 girls with an equal distribution across BMI range. Thus, data from a total of 180 children and adolescents will be included in the data set. Children will be recruited by flyers sent to faculty and staff at Brigham Young University (BYU). As an incentive to participate in this study and to improve the recruitment of children and adolescents, participating children will be given a \$5 Cinemark movie pass after completing this study.

Prior to recruiting participants and collecting data, the methods of this study and the informed consent process will be reviewed and approved by the Institutional Review Board (IRB) for the use of human subjects at BYU. Prior to participating in the study, each participant and his/her parent(s) will be informed of the procedures of this study. Participants will be asked to sign a consent form and his/her parents will be asked to sign a parental permission form to ensure informed consent (see Appendix A).

This study will be conducted as part of a children's study which involves two other thesis research projects. All three research projects will be conducted concurrently. There will be an overlap of participants, participant recruitment, and organization of data collection, and data entry. This study will collect carotid IMT data on all 180 participants. The body composition data collected in participants 12-17 years of age in another study will be used as descriptive data for this study and as an independent

variable in the statistical analysis. Carotid IMT data collected in this study will not be used in the other two studies.

Procedures

Appointments will be made with the parent or guardian of interested participants. Because participants' body composition and cardiorespiratory fitness will be assessed as part of the other two thesis projects, parents or guardians will be instructed to have their child(ren) wear athletic shorts and a t-shirt to their appointment. In addition, participants will be asked to avoid eating a meal or participating in vigorous physical activity for 3-4 hours prior to the scheduled appointment. Appointments for girls will be scheduled at a time when they are not menstruating. Participants will also have blood drawn at the Timpanogos Hospital. Parents or guardians will be instructed to have their child(ren) fast for 12 hours prior to the blood draw.

Apart from the principal measurement of carotid artery IMT, several other measurements which represent independent or confounding factors in carotid artery thickness will be taken on each participant. These measurements include height (cm), weight (kg), body mass index (BMI, kg/m^2), resting blood pressure, blood lipids and cardio-respiratory fitness (VO_2max).

Weight and height. Height (cm) will be measured and recorded for each participant using a calibrated wall scale to the nearest one-half centimeter. Weight will be measured and recorded for each participant using a digital scale (Ohaus Model CD-33, Ohaus Corporation, Pine Brook NJ, USA) to the nearest one-tenth of a kilogram. BMI will be calculated from measured weight and height values.

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Cardiorespiratory fitness. Cardiorespiratory fitness ($VO_2\text{max}$) will be measured in adolescents 12-17 years of age during a maximal graded exercise treadmill test (GXT). The GXTs will be completed as part of another study. $VO_2\text{max}$ values in children 12-17 years of age will be used as an independent variable in the statistical analysis of carotid IMT.

Resting blood pressure. Resting blood pressure will be measured on the left arm in the seated position following a minimum of 15 minutes of rest. The average of two systolic and diastolic blood pressure values will be recorded.

Blood lipid profile. Parents will be asked to take their child(ren) to Timpanogos Hospital to have blood drawn to determine plasma levels of triglycerides, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and total cholesterol (TC). Timpanogos Hospital will send blood lipid profile lab reports directly to the principal investigator. The blood lipid profile results will be shared with the participant. Participants will be instructed to fast for 12 hours prior to having their blood drawn.

Body composition. Body composition will be estimated in all participants. Body composition will be assessed using dual-energy x-ray absorptiometry (DXA). All DXA scans will be performed by a Utah State certified technician using a Hologic QDR4500 scanner (Hologic Inc., Bedford, MA) and software version 11.2 with supplemental pediatric software. Manufacturer recommended operating procedures for whole-body scans will be followed. Each scan will take about 7 minutes. Body composition will be reported as a percentage of body weight that is fat.

High-resolution carotid ultrasound. The methodology for the SonoCalc automated software analysis ultrasound system used in this study was described and validated by Fritz.²⁴ All images will be taken from the right common carotid artery using a Sonosite Titan Ultrasound system (Sonosite Inc., Bothell, WA). The Sonosite Titan system is an M-mode, high-resolution ultrasonograph, equipped with a 5-MHz transducer. Images from an anterior, direct, and posterior view will be captured to analyze the thickness of the arterial wall from three different angles. Each image of the right common carotid will be captured by the same technician.

Images will be captured at a point 1 cm proximal to the common carotid bifurcation. In cases where the carotid segment is unclear and the software is unable to identify the intima/lumen surface, a manual analysis will be performed by the process described by Fritz.²⁴ A trained researcher will analyze all images of the common carotid artery using the SonoCalc software system to determine the average IMT of the captured images for the 180 subjects involved in the study. The average carotid IMT will be used in data analysis.

Statistical Analysis

Statistical analysis will be performed using SPSS (Software Package for the Social Sciences) for Windows, Version 10.0 and SAS while maintaining the alpha level at $p < 0.05$. The strength of the relationship between body fat percentage (and other independent variables) and carotid IMT will be described using a correlation coefficient. The shared variance will be measured using an r-squared value. Potential confounding variables will be controlled for using the Proc GLM command in SAS. Using carotid

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IMT as the dependent variable, the strength of body fat percentage as an independent variable will be determined after controlling for other potentially confounding variables (i.e., height, weight, BMI, resting blood pressure, HDL-C, LDL-C, TC, triglycerides).

Appropriate interpretations of the data and conclusions will be made based on the findings of the data analysis.

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