

ASSOCIATIONS OF FATNESS AND PHYSICAL ACTIVITY WITH BLOOD PRESSURE
AND C-REACTIVE PROTEIN IN CHILDREN AND ADOLESCENTS

By

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ABSTRACT

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The high prevalence of overweight and obesity among children and adolescents and low proportion of youth meeting national physical activity guidelines are major public health concerns. The influence of fatness on the development of atherosclerosis and cardiovascular disease (CVD) risk factors, including elevated blood pressure and elevated C-reactive protein (CRP), have been well documented. The influence of physical activity on these same CVD risk factors is less understood, though physical activity is considered a cornerstone in the prevention and treatment of obesity and CVD risk factors. Although the independent relationships between physical activity and fatness on CVD risk factors have been examined, the combined association of fatness and physical activity with these risk factors is not well understood in children and adolescents. Therefore, the purpose of this dissertation was to examine the combined association (interaction) of fatness and physical activity with blood pressure and CRP in two large nationally represented samples of children and adolescents, one from the United States (National Health and Nutrition Examination Survey) and the other from the United Kingdom (East of England Healthy Hearts Study). The analysis from the United States included both blood pressure and CRP, while the analysis from the United Kingdom focused only on blood pressure.

In each sample, subjects were classified by fatness (normal weight, overweight, obese) via body mass index and physical activity level (least active, low active, active) via questionnaire or accelerometry. Analyses were conducted for the total sample and for age and sex categories

when appropriate. Main effects and the combined association (interaction) of fatness and physical activity were examined by analysis of covariance and multiple linear regression. Logistic regression was performed to determine the influence of age, sex, fatness, and physical activity on having high-normal blood pressure or high blood pressure.

Overall, fatness was consistently shown to have a positive relationship with blood pressure and CRP in both samples. Physical activity was inversely related with blood pressure and CRP consistently in girls, but not in boys. No combined association between fatness and physical activity with blood pressure was evident in the United Kingdom sample. However, there was a combined association between fatness and physical activity with blood pressure in the United States sample. Again, this relationship was seen consistently in girls, but not evident in boys. There was also a combined association between fatness and physical activity with CRP in the United States sample. This interaction was seen in both boys and girls.

The results of this study indicate that fatness has a strong influence on blood pressure and CRP. The combined association between fatness and physical activity with blood pressure and CRP is novel and highlights the importance of both factors when working to improve the overall cardiovascular health of children and adolescents. This relationship has been observed with aerobic fitness but the results of this study highlight that physical activity, both moderate and vigorous intensity, is beneficial.

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ABBREVIATIONS

ANCOVA	Analysis of Covariance
β	Beta Coefficient
BMI	Body Mass Index
CI	Confidence Interval
CDC	Centers for Disease Control and Prevention
CRP	C-Reactive Protein
CVD	Cardiovascular Disease
DBP	Diastolic Blood Pressure
HDL	High Density Lipoprotein
HEI	Healthy Eating Index
HTN	Hypertension
IOTF	International Obesity Task Force
MAP	Mean Arterial Pressure
METS	Metabolic Equivalent
mg/L	Milligram per liter

mL	Milliliter
ml/kg/min	Milliliter/Kilogram/Minute
mmHg	Millimeter of Mercury
MVPA	Moderate- to Vigorous Physical Activity
NHANES	National Health and Nutrition Examination Survey
OR	Odds Ratio
PACER	Progressive Aerobic Cardiovascular Endurance Run
PAQ	Physical Activity Questionnaire
PAQ-A	Physical Activity Questionnaire – Adolescents
PAQ-C	Physical Activity Questionnaire – Older Children
SBP	Systolic Blood Pressure
UK	United Kingdom
U.S.	United States
VO ₂ max	Maximum Volume of Oxygen Consumed

INTRODUCTION

Overall Purpose and Structure. The overall purpose of this dissertation (and the theme of my line of research) is to better understand the inter-relationships among physical activity, adiposity, and the vascular health of children and adolescents. This dissertation is presented in the form of two manuscripts (listed below), which build upon my previous research, and address the overall research question and expand the current literature on this topic. This introduction provides a brief, general overview of the topic. An extended literature review is presented in Chapter 1. The two manuscripts follow in Chapters 2 and 3, with Chapter 4 providing an overall summary, a discussion of whether the aims and hypotheses were supported or not, and recommendations for future research.

CHAPTER 2 – Physical activity, adiposity, and vascular health in U.S. children and adolescents: NHANES 2003-2006.

CHAPTER 3 – Physical activity, adiposity, and resting blood pressure in a large sample of 8-18 year olds: The East of England Healthy Hearts Study.

Background and Rationale. Obesity is a challenging and complex health problem in the United States (U.S.) and throughout the world. The complexity of the problem is compounded by the fact that obesity is influenced by a host of biological, psychological, and social factors including: genetics, maternal and fetal factors, physical (in)activity, diet, socioeconomic status, emotional/psychological health, physiological conditions, hormones, food marketing and advertising, urban planning, and more (1). It is well-documented that the prevalence of obesity in

the U.S. and globally, has increased substantially in the past few decades in both adults and children (2, 3). In the United States, the prevalence of overweight in children tripled during the period of 1980 to 2000 (4). Current estimates indicate that 32% are at or above the 85th percentile, 17% are at or above the 95th percentile, and 12% of children and adolescents are at or above the 97th percentile for body mass index (BMI) (2). BMI is often used as a proxy for a measure of fatness and will be used as such in this dissertation.

A major concern related to the high prevalence of overweight and obesity among children and adolescents is an adverse cardiovascular disease (CVD) risk factor profile, including elevated blood pressure and impaired endothelial function (5, 6) – the latter often indicated by C-reactive protein (CRP), a biomarker of acute phase tissue inflammation (7). Excess body fat is a major risk factor for the development of atherosclerotic plaque (8) and elevated blood pressure (9-12), and the development of atherosclerotic lesions has clearly been shown to begin early in life (13, 14). Obesity and elevated blood pressure during childhood is problematic given that both track into adulthood (15), and both are related to increased rates of CVD mortality and morbidity (16, 17).

Since a large percentage of the population faces a future of overweight and obesity, which is linked to cardiovascular disease risk, researchers need to address these maladies from many angles, including highlighting the importance of physical activity and healthy nutrition choices in the school and home environments. A primary strategy in the prevention of atherosclerosis, and weight loss/weight maintenance, is to achieve the daily recommendation for physical activity. Physical activity recommendations for children and adolescents advise 60 minutes per day of moderate-to-vigorous physical activity (MVPA), which should include

vigorous-intensity physical activity at least three days a week (18). Estimates from the 2003-2004 NHANES indicated that 42% of U.S. children aged 6 to 11 years and only 8% of 12 to 19 year olds met these physical activity guidelines (19). Estimates of children from the United Kingdom (UK) meeting these same recommendations are much lower, with 5.1% of boys and 0.4% of girls age 11 accumulating 60 minutes of MVPA a day (20). The low prevalence of physical activity coupled with the high prevalence of overweight and obesity is a combination that increases the prevalence and severity of CVD risk.

Researchers have examined the independent relationships between fatness and physical activity with factors such as blood pressure, CRP, and endothelial function in children and adolescents. Collectively, these three factors (blood pressure, CRP, and endothelial function) can be grouped together as markers of vascular health. Previous studies have shown independent relationships between fatness and blood pressure, CRP, and impaired endothelial function (21-24). In general, there is a moderate, positive relationship between fatness and these markers of vascular health (10, 25-34). Physical activity has also been shown to have independent relationships with these same markers. A weak inverse relationship between physical activity and blood pressure (24) has been shown in children and adolescents. Although the relationship between physical activity and CRP has not been examined as thoroughly as it has between physical activity and blood pressure, results have been mixed with studies showing no relationship (35, 36), a positive relationship (37), and an inverse relationship (26, 38, 39). The independent relationships between both fatness and physical activity and these markers of vascular health underscore the importance of focusing on decreasing fatness and improving the amount of physical activity performed regularly by children and adolescents

Various factors, both environmental and genetic, can influence blood pressure and CRP levels. Age and gender are two important considerations in these relationships. Both animal (40, 41) and human studies (42-44) have shown that blood pressure in males is consistently higher than pre-menopausal women of similar age. This sex difference diminishes with age, as women in their 60's and 70's have a higher likelihood of being diagnosed with hypertension post-menopause than pre-menopausal women (45). The prevalence of hypertension has been shown to increase with age. It is estimated that greater than 50% of adults age 60 to 69 years and 75% of those over the age of 70 years have hypertension (46). Age and gender differences in CRP levels have not been examined as extensively as they have been with blood pressure, but a trend for higher levels of CRP in women compared to men has been identified, with this difference appearing during the time of puberty (47). In addition to gender differences, ethnic differences in CRP levels have also been identified (48). The positive relationship between CRP levels and age has been examined, and while there appears to be an age-related change in CRP levels, it has also been noted that the increase in visceral fat that often accompanies aging might be the primary cause of this increase in CRP (49). Examining the relationships of age and gender on blood pressure in children and adolescents may assist in better understanding these relationships in adulthood and the effect they have on the overall risk of CVD.

With the current prevalence of overweight and obesity in children and adolescents, combined with the low prevalence of children and adolescents meeting the physical activity guidelines, understanding how adiposity and physical activity influence each other and their interactive effects on blood pressure and CRP levels is important to obtain a more complete view on mechanisms and potential treatments. Few studies have examined the combined association of fatness or weight status (BMI) and physical activity on CVD risk factors in youth. Previous

work has examined the combined association of fatness and aerobic fitness, rather than physical activity, on CVD risk factors. Building on the work of Blair and colleagues in adults (50, 51), these studies in children and adolescents (52-55) clearly showed that aerobic fitness attenuated the influence of fatness on components of metabolic syndrome, including blood pressure. While aerobic fitness and physical activity have been shown to be moderately associated in children and adolescents (56, 57), they are different constructs. Specifically, aerobic fitness is a physiological and anatomical trait that integrates the cardiovascular and respiratory systems with oxidative properties of the skeletal muscles, whereas physical activity is a behavior defined as any bodily movement produced by skeletal muscles that results in an increase in energy expenditure over resting levels (58). While understanding the combined association of fatness and aerobic fitness with CVD risk factors is important, public health guidelines for both adults and children are focused on physical activity, not aerobic fitness. Due to the focus on physical activity and the current prevalence of overweight and obesity, a clear understanding of the combined association of physical activity and fatness is necessary.

It is clear that obese children and adolescents are being diagnosed with CVD risk factors, including hypertension (59) and diabetes (60), before they reach adulthood. Overweight and obesity have been shown to track from childhood into adulthood (61-63), so dependence on weight loss as a key in the treatment of CVD risk factors seems impractical. Additionally, examining the combined association of fatness and physical activity is important, as there are overweight and obese children and adolescents meeting the physical activity guidelines (fat-active) (64, 65). Understanding how meeting the physical activity guidelines influences CVD risk factors in overweight and obese children and adolescents, without change in weight status,

may provide better guidance to primary care physicians who treat these youth and assist in creating more effective interventions.

To investigate whether physical activity influences the relationship between fatness and CVD risk factors, namely blood pressure and CRP, our previous work investigated the combined association of physical activity and fatness on blood pressure and CRP in two Midwestern cohorts of children (66, 67). In both cohorts, null results were found – that is, physical activity did not influence the relationship between fatness and blood pressure or CRP. The lack of significant results may have been due to a number of methodological limitations, including the classification of physical activity in the first cohort. Children were categorized as meeting or not meeting the recommendations of 60 minutes of MVPA per day. Although physical activity was measured objectively by accelerometry, we were not able to categorize by a variety of physical activity levels due to the small sample size ($n=157$). In a larger sample, we would ideally investigate this relationship either by categorizing the children as active (>60 minutes of MVPA per day), low active (15-59 minutes of MVPA per day), and least active (<15 minutes of MVPA per day), or by examining physical activity as a continuous variable. In the second cohort, physical activity was self-reported by questionnaire. A more sophisticated, objective measure of physical activity may have led to more accurate classification of those children who were meeting the physical activity guidelines. A final limitation was the low prevalence of elevated blood pressure in both cohorts. The overall prevalence of elevated blood pressure in children and adolescents has been reported as 1-3% in one study (68), but an increase in the trend of children and adolescents being diagnosed with elevated blood pressure has been noted (69), with one study reporting a prevalence of 4.5% in a cohort of 5100 children, many of whom were racially and ethnically diverse (70). Additionally, in a cohort of 6,790 11 to 17 year olds, 3.2% were

classified as hypertensive, with an additional 15.7% pre-hypertensive. The risk of being classified as hypertensive increased with an increase in BMI (71). While these previous studies sought to investigate the combined association between fatness and physical activity on blood pressure and CRP, the limitations in measurement and study sample may have made finding any true association difficult. By identifying these limitations, future work can make the appropriate changes to better answer the research question and identify any combined association between physical activity and fatness on blood pressure and CRP levels. Therefore, this dissertation will build upon our previous work, address the limitations of measurement and sample size by using two large nationally representative cohorts – one from the UK and one from the U.S., and investigate the combined association (interaction) of physical activity and fatness on two markers of vascular health – blood pressure and CRP.

Aims and Hypotheses. The aims and hypotheses of this dissertation include:

Aim 1: Examine the independent and combined associations of physical activity and fatness with blood pressure.

Hypothesis 1A: There will be an inverse relationship between physical activity and blood pressure.

Hypothesis 1B: There will be a positive relationship between BMI and blood pressure.

Hypothesis 1C: There will be a combined association (interaction) between physical activity and adiposity with blood pressure.

Aim 2: Examine the independent and combined association of physical activity and fatness with CRP.

Hypothesis 2A: There will be an inverse relationship between physical activity and CRP.

Hypothesis 2B: There will be a positive relationship between BMI and CRP.

Hypothesis 2C: There will be a combined association (interaction) between physical activity and fatness with CRP.

Aim 3: Examine the relationship of age with blood pressure.

Hypothesis 3A: Older youth will have higher measurements of blood pressure than younger youth.

Aim 4: Examine the relationship of gender with blood pressure and CRP.

Hypothesis 4A: Boys will have higher measurement of blood pressure than girls.

Hypothesis 4B: Girls will have higher measurement of CRP than boys.

Strengths and Significance. This dissertation will serve to address the limitations of my previous work including sample size, measurement instrumentation, and the low prevalence of obese individuals and those with elevated blood pressure and CRP. Results from this study will increase our knowledge of the combined association of physical activity and fatness with blood pressure and CRP, two CVD risk factors that are becoming more prevalent, particularly in a younger, obese population. Additionally, this work will give greater insight into the phenomenon of fat-active children and adolescents. While the proportion of fat-active children and adolescents is low (64, 65), it is still a segment of the population that needs to be better

understood, as it has been shown that weight status tracks from childhood and adolescence, into adulthood. Often times, improvement in this population is measured in pounds or inches lost. By better understanding the interplay between physical activity and fatness, interventions can focus more on improving physical activity instead of solely focusing on weight loss. The use of two large cohorts will allow for stratification by age, sex, and physical activity level, providing a comprehensive examination of the combined association between fatness and physical activity. These two manuscripts will add to the current literature on the relationship between physical activity and fatness, and combined, they will give a greater depth and context to what is known about children and adolescents who are fat-active, which may help better define interventions to help improve their cardiovascular health.

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CHAPTER 1

LITERATURE REVIEW

This literature review provides the reader with background on several aspects of vascular health including: what it is, how it develops, how it is measured, and how adiposity, physical activity, and diet in children and adolescents influence it.

I. VASCULAR HEALTH

I.A. Definition and Measurement

The vascular system is comprised of arteries, arterioles, capillaries, venules, and veins. Oxygenated blood flows out of the heart, through the aorta, into the systemic arteries and arterioles, and finally to the capillaries where the exchange of oxygen, carbon dioxide, nutrients, and hormones take place. The venules and veins return the deoxygenated blood back to the heart, and eventually the lungs, so it can once again nourish the body's tissues. Both arteries and veins are comprised of layers of tissue (tunica intima, tunica media, and tunica adventitia), but these layers are thinner and less elastic in veins compared to arteries. The smooth muscle layer in arteries allow for greater elasticity and better shunting of the blood throughout the body, especially during times of physiological stress, which exercise or physical activity could be considered. The vessels that comprise the vascular system, as a whole, would stretch 60,000 miles if laid out end to end (1).

There is no one universal definition of vascular health. A number of measures can be used to quantify the health of the vascular system and depending on the population being studied, the age and medical history of that population. Typically, blood pressure, endothelial measures,

and C-reactive protein (CRP) have been addressed in existing literature, either separately or in combination, to quantify the health of a child/adolescent's vascular system. Due to this, this dissertation will be focused on two of those measures, namely, blood pressure and CRP. Blood pressure is perhaps the most common measure of vascular health. Blood pressure measures the pressure of the blood in the arteries at two time points – contraction of the heart (systole) and relaxation of the heart (diastole). Increased blood pressure can lead to damage to the endothelial lining of the blood vessels, which can then lead to the development of lesions and the formation of plaque along the artery walls. Due to the effect of growth and maturation on the size and stature of a child or adolescent, single cut-points are not used when determining the hypertensive status in children or adolescents. Instead, hypertension in children and adolescents is defined as an average systolic blood pressure and/or diastolic blood pressure that is equal to or above the 95th percentile for gender, age, and height on three or more occasions. Pre-hypertension is defined as an average systolic or diastolic blood pressure that is equal to or above the 90th percentile for gender, age, and height but below the 95th percentile. An adolescent with a blood pressure greater than 120/80 mmHg is considered to be pre-hypertensive regardless of whether that value falls below the 95th percentile. The accuracy of measuring a child or adolescents' blood pressure relies on the type of equipment used and the proper sizing of that equipment. Auscultation is preferred over oscillometric devices because of variability that can come from improper or failed calibration of the oscillometric devices. The size and placement of the blood pressure cuff on a child is extremely important and many cuffs that are designed for children are made to accommodate a wide range of arm sizes in children. A child diagnosed as hypertensive needs closer evaluation to determine the level of hypertension (stage 1 or 2) and whether they

have primary (essential) or secondary (primarily caused by renal disease) hypertension, as the treatments vary based on those two distinctions (2).

The endothelium is a dynamic structure that can be examined non-invasively through measuring the ability of the vessels to dilate with increased blood flow. Flow-mediated dilation measures the vasodilatory capacity of the brachial artery after a bout of ischemia induced by superinflation of a blood pressure cuff. Due to the non-invasiveness of the procedure, flow-mediated dilation can be easily performed on children and adolescents. Ultrasound images of the diameter of the brachial artery are taken prior to the blood pressure cuff being inflated and once the cuff is released, and the increase in diameter following release is measured. A cut point of 10% is often used as the delineation between a normal response and an impaired response, meaning that an increase in brachial artery diameter less than 10% greater than the resting measure would be an impaired response (3). The brachial artery is often used as a proxy for the coronary arteries (4).

Finally, CRP, a blood biomarker, can be used as a marker of inflammation in the vessels. CRP is a protein that is released by the liver in response to increases in interleukin-6, a proinflammatory cytokine produced by adipocytes. A substantial increase in CRP (>10 mg/L) can be attributed to various disease states such as asthma, systemic infection, etc., but more frequently it is used to detect low-grade vascular inflammation, which is known to occur during the atherosclerotic process. Guidelines for appropriate levels of CRP in adults have been set jointly by the CDC and the American Heart Association. Cut points that relate to a low, moderate, or high risk of a future cardiovascular event are <1 mg/L, 1-3 mg/L, and >3 mg/L, respectively. Cut points in children have not been developed, which leads many researchers to use the adult values when studying children (5). CRP measurements can be determined by both a

venous blood draw and a fingerstick, which allows for use in field-based studies, such as school-based interventions. The correlation between fingerstick measurement and core laboratory measurement for CRP was 0.81 in a previous investigation (6).

These three measures (blood pressure, flow-mediated dilation, and CRP) used in combination, with or without additional measures, such as total or low-density lipoproteins, can be used to construct a more complete picture of vascular health than when used on their own. Measuring the vascular health of children is increasingly gaining importance as researchers strive to better understand the origins of atherosclerosis, and gain more information indicating that the development of fatty streaks and plaque begin in childhood, if not infancy.

I.B. Development of Atherosclerosis

The formation of atherosclerotic plaque is a process that has been found to be the primary cause of heart attacks and strokes (7). The development of an advanced atherosclerotic lesion is preceded by a series of morphological changes that take place in response to the effects of cardiovascular disease (CVD) risk factors, in addition to mechanical forces that occur due to shear stress placed on the vessel wall. As outlined by Stary et al. (8), these changes can be grouped and categorized into three distinct lesion types – type I, II and III. It has been shown, from the work of both Stary et al. and Ross (7), that atherosclerotic lesions begin developing in childhood. The rate and degree of progression is dependent on the environmental and genetic factors of individuals. The age at which plaque appears in the coronary arteries and the pace of the plaque development are important factors to consider when determining the best age to begin risk factor interventions to delay the onset of symptoms and progression of the disease.

I.C. Early Origins of Atherosclerosis

The clinical manifestations of atherosclerosis often develop in later life, with the occurrence of myocardial infarctions, strokes, and aneurysms, but the development of the atherosclerotic plaque begins formation much earlier in life. Research has focused on infants, children, adolescents, and young adults to better understand how the formation and progression of atherosclerotic plaque occurs during the early part of life and what factors – both environmental and genetic – influence its development.

McGill et al. (9) examined the coronary arteries of 2876 15- to 34-year olds who died of non-cardiovascular causes (accidents, homicides or suicides) over a seven-year period. There were significant differences associated with increasing age, gender, and ethnicity in regard to all three types of plaque formation, with those in the older age category, males, and blacks having greater prevalence of fatty streaks and a greater percentage of surface area involved with the fatty streaks. Additional factors that were examined were non-HDL cholesterol levels, HDL-cholesterol levels, and obesity. Obesity had no association with plaque formation in females but a significant association with all three levels of plaque formation in males. When grouped as low risk (normotensive, nonsmoker, non-HDL <160 mg/dL, HDL $\geq$ 35 mg/dL, and body mass index (BMI) < 30 kg/m²) and high risk (hypertensive, smoker, non-HDL $\geq$ 160 mg/dL, HDL < 35 mg/dL, and BMI $\geq$ 30 kg/m²), those considered high risk had more extensive flat fatty streaks, raised fatty streaks, and raised lesions in all age groups except the 15- to 19-year group. As has been seen in other studies, the progression of the fatty streak to the raised fatty streak to the raised lesion is related to age and the rate of this progression appears to increase when combined with the influence of established CVD risk factors (7, 8).

Nakashima et al. (10) also examined coronary arteries during autopsy to better clarify the features of early coronary artery lesions. The right coronary arteries from 38 subjects between the ages of 7 and 49 years old were examined upon death from non-coronary heart disease causes. The results supported the “response-to-retention” hypothesis that states that lipoproteins bind and stay in the intimal layer of the vessel at the first stage of lesion development. The thickening of the intimal layer and the subsequent development of the fatty streak by way of laying down lipids in the thickened intima were thought by the authors to be the earliest form of coronary atherosclerosis. As the lipids accumulate in the intimal layer, the amount of encroachment into the lumen increases, increasing the narrowing of the vessel. The build up of lipids can be traced to both environmental factors (diet) and genetics (hypercholesterolemia), which can accelerate the progression. As further work examines epigenetic mechanisms, clarification of this relationship will allow for better prevention methods and programs that target the reduction of risk factors.

A Finnish research group investigated the relationships between various factors and intimal thickening in a cohort of Finnish infants and children who died between the ages of 0 and 15 years. To investigate the relationship between intrauterine growth retardation and intimal thickening in the coronary arteries, Pesonen et al. (11) examined the autopsy results from 111 subjects who died within the first month of life (mean postnatal age = 6 days). By limiting the subjects to the first month of life, environmental factors that could influence the intimal medial thickness, should have been minimized. The results showed that there was no association between small birth size and intimal thickness in this cohort of low-birth weight infants. This contradicts other research that has shown an increase intimal thickness in young adults who suffered from intrauterine growth restriction and exaggerated growth postnatally. The authors

concluded that while low birth weight was not shown to be associated with intimal thickening, the restricted growth prenatally might still be associated with endothelial dysfunction and injury, which has been shown to cause atherosclerotic plaque formation in children and young adults as demonstrated by Ross (7).

The early development of atherosclerotic lesions and the subsequent dysfunction that occurs from disruption of the laminar flow of blood through the arteries is a concern as it has been clearly shown that this progression begins early in life. Understanding ways to modify this relationship in children and adolescents before permanent damage of the endothelium is done, needs to be a priority as the prevalence of CVD risk factors in children and adolescents, especially those who are obese, is increasing.

II. OBESITY

II.A. Obesity in Children and Adolescents

Recent estimates from the National Health and Nutrition Examination Survey (NHANES) indicated that 12% of children and adolescents are at or above the 97th percentile for BMI, 17% are at or above the 95th percentile, and 32% are at or above the 85th percentile (12).

BMI is often used as a proxy for fatness in large epidemiological studies in both adults and children. The practicality of using a criterion method (e.g., hydrostatic weighing, dual-emission X-ray absorptiometry, etc.) is often overshadowed by the cost and the accessibility of such a device. BMI is a measure of the relationship between body weight and body height that does not differentiate between muscle mass, fat mass, or skeletal mass, and has been shown to produce errors when estimating body fatness (13). While adult BMI is classified by discrete cut points,

the same practice is not used with children and adolescents. The 2000 Centers for Disease Control (CDC) Growth Charts, which are currently used to identify and classify a child's BMI percentile, were developed from National Health Examination Surveys II and III from the 1960s, and the National Health and Nutrition Examination Study (NHANES) I and II in the 1970s. Obese is classified as a BMI greater or equal to the 95th percentile and overweight is classified as the 85th percentile to the 94th percentile.

The relationship between BMI and a measure of body fatness has been examined in adults and children. In adults, BMI has been shown to moderately correlated with body fatness ($r=0.75$) (14). The correlations in studies focusing on children and adolescents have varied depending on the fatness level of the children being examined. Schaefer et al. reported that the relationship between BMI and skinfold thickness in thin boys was very low ($r=0.01$), while much higher in boys with more fat mass ($r=0.58$) (15). Research from the Pediatric Rosetta Project has corroborated this finding and has shown that when focusing on a population with higher body fat, BMI is a good tool for classifying children correctly as obese (16, 17). In this study BMI was shown to have a positive predictive value of 73% in boys and 75% in girls, a sensitivity of 74% and 75% for boys and girls, respectively, and a specificity of roughly 95% in both boys and girls. Unfortunately, when examining the positive predictive value, sensitivity, and specificity in children who fall between the 85th percentile and the 94th percentile, the values were not as strong, with roughly 30% of those children having body fat measurements comparable to children considered to be of normal fatness. Although BMI has limitations to its use, the ability to classify children and adolescents who might be at risk for having excessive body fat and an

elevated disease risk is an important tool in risk stratification and development of intervention programs.

II.B. Obesity, Blood Pressure, and CRP

Adverse CVD risk factors such as elevated blood pressure and impaired endothelial function (18-23) have been identified in children and adolescents who are overweight or obese. The positive relationship between fatness and blood pressure has been shown to be strong (24-27). An increase in both total fatness and visceral fatness was shown to be significantly related to an increased ambulatory systolic blood pressure and diastolic blood pressure compared to lean controls (25) and the number of overweight and obese children with blood pressure values below the 50th percentile were much lower than those children of normal weight (27). Results from NHANES 1988-2006 (28) indicated that weight status was significantly associated with elevated blood pressure in 8-12 year old children with overweight boys (OR 1.54, CI = 1.11-2.13) and obese boys and girls (OR 2.81, CI = 2.13-3.71 and OR 2.55, CI = 1.75-3.73, respectively) being significantly more likely to be pre-hypertensive than normal weight youth. The likelihood of being hypertensive was also significantly greater in both overweight and obese boys (OR 6.06, CI = 2.73-13.44) and obese girls (OR 2.33, CI = 1.31-4.13). The association between obesity and blood pressure in children and adolescents has been clearly demonstrated in various ethnic groups, in both genders, and when taking fitness and activity levels into account (20).

As with other functions of the body, blood pressure follows a circadian rhythm and fluctuates between daytime and nighttime measurements. Torok et al. (29) investigated a phenomenon called “dipping” in regards to blood pressure measurements taken in a group of seventy-three obese children. In healthy individuals, blood pressure dips substantially at night

(dippers) compared to values measured during the day. Previous work has shown that within certain populations, some individuals do not obtain this drop in nocturnal blood pressure (non-dippers), which has been linked with higher cardiovascular complications and organ damage. The findings showed that 42% of the obese children were non-dippers. There was no significant difference between dippers and non-dippers in degree of obesity, any of the lipid or glucose measurements, or prevalence of hypertension when office blood pressure measurements were used. When ambulatory blood pressure measurement was considered, the prevalence of hypertension was significantly higher in the non-dippers. Exercise capacity was also measured at heart rates of 130, 150 and 170 beats per minute and values were significantly lower in non-dippers. More research needs to be done to further explain the difference between the dippers and non-dippers and how this lack of circadian rhythm related to blood pressure affects endothelial function, exercise capacity, left ventricular hypertrophy, and renal function.

CRP has also been shown to be elevated in overweight children (30-32). In studies of both children and adults, a high level of CRP has been shown to be associated with increased BMI, visceral adiposity, insulin resistance, endothelial dysfunction and hypertension (22, 33, 34). CRP has also been shown to be positively correlated with systolic and diastolic blood pressure in overweight and obese children (21). There has been debate as to whether puberty accelerates endothelial dysfunction or if the endothelial dysfunction is already present when an obese child reaches this stage of development. Aggoun et al. (23) and Giannini et al. (35) both sought to answer this question by documenting flow-mediated dilation and intimal medial thickness, respectively, in groups of pre-pubertal children. Aggoun et al. (23) revealed that flow-mediated dilation was impaired in obese children (Tanner stage 1) and inversely related to BMI and fat mass. There was no significant increase in intimal medial thickness, even with the

endothelial dysfunction detected. Giannini et al. (35) examined intimal medial thickness and inflammation by use of CRP in obese children (Tanner stage 1) but, unlike Aggoun et al. (23), did find significant differences in intimal medial thickness between obese children and lean children. The obese children also showed significantly higher CRP levels compared to lean controls. The difference between the outcomes in these two studies may be due to the small sample sizes in both studies. Also, the obese children in the study by Aggoun et al. (23) were heavier and had larger waist circumferences and possibly more fat mass than those subjects in the study by Giannini et al. (35).

The relationship between increased fatness and blood pressure, CRP, and impaired endothelial function, separately, has been shown to be strong (25, 36-45). These studies have been both cross-sectional (25, 37, 38) and randomized controlled trials. With the current prevalence of overweight and obesity in children and adolescents, in addition to the tracking of overweight and obesity from childhood into adulthood, a major public health crisis is upon the United States (U.S.). Children and adolescents being diagnosed with elevated blood pressure, diabetes, and endothelial dysfunction will live longer with these diseases than today's adults. Examining factors that can help attenuate the influence of obesity on CVD risk factors is important to better understand how to treat the co-morbidities that travel in constellation with overweight and obesity.

The influence of obesity on vascular health is well documented and is a public health concern. Further research needs to concentrate on interventions to decrease overall fatness, in addition to increase daily physical activity and improve the overall quality of the diet of children and adolescents.

III. PHYSICAL ACTIVITY

III.A. Physical Activity in Children and Adolescents

An important distinction must be made when considering the concepts of physical fitness (or more specifically aerobic fitness) and physical activity. Aerobic fitness, which is best represented by the maximal oxygen consumption ($\text{VO}_{2\text{max}}$), involves the integrated efforts of the cardiovascular and respiratory systems along with the oxidative properties of skeletal muscle. Thus, aerobic fitness is a physiological trait. On the other hand, physical activity is a behavioral trait defined as any bodily movement produced by skeletal muscles that results in an increase in energy expenditure over resting levels (46). Although both are related to CVD risk factors, the mechanism by which they influence these risk factors differs (47).

National physical activity recommendations for children and adolescents released in 2008 advise 60 minutes per day of MVPA and should include vigorous-intensity physical activity at least three days a week. Troiano et al. (48) analyzed accelerometry data from the 2003-2004 NHANES and determined that 42% of children aged 6-11 years met the national physical activity guidelines of 60 minutes per day, while only 8% of adolescents (12 to 19 years) met guidelines.

III.B Physical Activity Measurement.

Physical activity can be measured by criterion, subjective, and objective measures. Criterion measures, such as direct and indirect calorimetry, doubly labeled water, and direct observation can be used with children, but the cost and burden, both on the subjects and the researchers, makes the practicality of using these methods difficult. Subjective measures,

including self-report, are commonly used in assessing habitual physical activity. The Youth Risk Behavior Surveillance System, a nation-wide school-based survey that is conducted by the CDC, monitors health behaviors among youth and includes seven questions regarding physical activity. Included is the following self-report question: “During the past 7 days, on how many days were you physically active for a total of at least 60 minutes per day?”. This type of question is commonly used in surveys and questionnaires regarding habitual physical activity (49). Self-reported physical activity can easily be used for large epidemiological studies with both adults and children. The lower age range for children to understand and be able to report on their level of habitual physical activity has been examined (50) and while age and the ability to recall past behavior are both limitations when relying on self-report, it is a more feasible way of obtaining a measure of habitual physical activity than some of the more costly criterion methods. Objective measures of quantifying habitual physical activity have been gaining prominence in the study of activity and children. Pedometers (51) and accelerometers (52) have become common tools in studies focusing on physical activity and children. Combining subjective and objective methods of measurement may help alleviate some of the limitations of the individual methods while increasing the depth of the information collected.

The type of measurement tool used to quantify physical activity can have an impact on the outcome of a study. Often with large epidemiological studies, self-reported physical activity data are used, as it is a more feasible and economic means to collect large quantities of data. The limitation of using self-report physical activity data is that the accuracy is dependent on the subject’s recall of, in most cases, the last seven days of activity. Additionally, the subject is asked to determine intensity of activity. This might be difficult for some children and adolescents. The use of accelerometers and pedometers, while a more objective measure, also

can be challenging, as it is dependent on the subject wearing the device over the appropriate number of days and for the adequate number of hours. If worn correctly, the data can reveal not only the amount of physical activity performed, but in the case of accelerometers, the intensity as well. Understanding the various methods in measurement of physical activity can assist in determining the best way to capture physical activity data to answer a specific research question.

III.C. Physical Activity, Blood Pressure, and CRP

Five studies examined the relationship between habitual physical activity and CRP and endothelial function in children and adolescents (38, 53-56). There was a wide variety in methodology among these five studies, which may have lead to the inconsistency in findings between them. Three studies showed positive associations between level of physical activity and endothelial function. All three used different methods of quantifying physical activity, from doubly labeled water (38), to the use of an Actigraph accelerometer (54), to a self-administered questionnaire (53). With such a wide variety in measures of physical activity, one would expect a wider range of outcomes, but all three had the same conclusion regarding physical activity and its positive effect on endothelial function. Hopkins et al. (54) investigated the relationship between endothelial function in the brachial artery, body composition, aerobic fitness, and physical activity in 129 9-10 year olds. Significant correlations were found between endothelial function and body fat percentage, aerobic fitness and MVPA. The strongest relationship was identified between intensity of physical activity and endothelial function in those subjects in the lowest flow- mediated dilation tertile. The authors concluded that interventions should focus on increasing the level of high intensity physical activity in which children participate instead of focusing on improving aerobic fitness or reducing body fat percentage if the goal is to improve endothelial function in those at high risk for cardiovascular disease. Increasing physical activity

versus improving aerobic fitness is an important distinction made by Hopkins et al. as the mechanisms behind both differ. By targeting behavioral modification (increasing physical activity) instead of physiological outcomes (aerobic fitness), it may be possible to improve the desire of a child to move from a lifetime of sedentary behavior to one of regular physical activity and exercise. This will bring obvious improvements to both endothelial function and CVD risk factors and lower overall risk for cardiovascular disease and other co-morbidities.

The two studies that were inconsistent in their findings regarding physical activity and endothelial function had different study designs, one being an observational longitudinal cohort study and one being a cross-sectional study design (55, 56). In addition, the study by Metcalf (55) used accelerometry data collected at four annual time points to calculate an average physical activity level for each subject. Since these children were age five years at baseline and age eight at the final measure and the average was used in the analysis, one must question whether there was a change in level of physical activity due to the effects of starting school and if this played a role in the outcomes. Platat et al. (56) used a questionnaire to calculate the number of Metabolic Equivalent (MET) hours per week. While one of the positive association studies used a similar method to quantify physical activity (53), the authors did describe one potential limitation that may have led to the inconsistent result. While the sample size of 640 adolescents was impressive, there was a low level of variability in CRP levels across that sample. This homogeneity may have made it difficult to detect any relationship between CRP and physical activity.

There has been a very consistent relationship between exercise training and improvement in both CRP and endothelial function, even with differences in length of intervention (six weeks to six months), inclusion of diet intervention or not, and type of exercise intervention used (circuit training, walking, swimming) (39-45). Three of these studies employed a crossover

design to investigate whether the improvements in endothelial function were reversible after the cessation of exercise training (43-45). In these studies, an increase in total fatness and visceral fatness were shown to be positively correlated with levels of CRP ($r=0.64$; $p=0.001$) (39), and impaired endothelial function (measured by flow mediated dilation) in overweight and obese children and adolescents compared to lean controls ($6.0\%\pm0.69\%$ vs. $12.32\%\pm3.14\%$) (45). In all three crossover studies, the improvements seen with the exercise training were reversed with detraining. This underscores the point that life long changes, extending past an intervention study, need to be stressed to children and their parents as a way to reduce the CVD risk that comes with decreased endothelial function or increased CRP levels.

There was one randomized controlled trial with exercise training that did not support the results of the other studies (36). This study may not have produced consistent results due to some limitations in methodology, including the attendance criterion of only 40% of all exercise sessions and the exercise dose ranging from 17 minutes to 61 minutes. This inconsistency of both dose and duration of exercise may have lead to the inconsistency in results.

Exercise training and physical activity have been shown to have a significant association with endothelial function in children and adolescents. Further understanding is necessary to better define the dose of physical activity needed, along with the intensity necessary, to see more consistent results, as are seen with exercise training studies.

IV. DIET

IV.A. Dietary Patterns in Normal, Overweight, and Obese Children and Adolescents

When comparing dietary patterns in normal weight and overweight or obese children or adolescents, it is clear that there is a lack of consensus on overall trends, intake of

macronutrients, and intake of specific food or food groups. An imbalance in energy intake versus energy expenditure is often cited as the basis for obesity, so it would be logical that there would be a clear difference in total energy consumption between normal weight and overweight or obese children or adolescents. In studies of adolescents, that relationship between weight status and total energy consumption has been inconsistent. A number of studies have shown no difference in total energy intake between weight status groups (57-59), while others have shown differences in total energy intake between weight status groups (60-62), and a recent study of adolescents from Greece reported an inverse relationship between total energy consumption and weight status (63). A number of confounders might be making this relationship unclear, including over or under-reporting of total energy consumed (64), the method or tool used to measure energy consumption, and a desire to lose weight by those who are overweight or obese. The variance ratios for nutrient intakes in children and adolescents have been reported to be up to two-fold greater than those reported in adults. (65)

When examining the diets of normal weight and overweight or obese youth, consumption of each macronutrient needs to be explored, not just total energy consumption. Increase in total fat consumption has shown to be related to poorer quality of diet (60, 63, 66) and also associated with measures of fat mass (BMI, skinfold) (67-69). Data regarding consumption of protein and carbohydrates has shown conflicting results between normal weight and overweight or obese adolescents. Ortega et al. (57) reported that the overweight/obese subjects consumed more of their energy from protein and fats and less from carbohydrates compared to the normal weight controls, while Hassapidou et al. (63) reported that the overweight/obese subjects in a cohort of Greek adolescents consumed less fat, protein, and carbohydrates compared to normal weight adolescents. Gazzaniga et al. (70) examined the association between body fatness and dietary

intake in 9-11 year old children and reported an inverse relationship between carbohydrate intake and percent body fat (adjusted for body weight). Intake of fiber has a beneficial impact on both fat and carbohydrate consumption as shown by data from the Bogalusa Heart Study (71). Those children and adolescents who consumed the greatest amount of fiber had lower consumption of total and saturated fat and higher consumption of carbohydrates. Unfortunately, intake of fiber is often well below the current dietary recommendations in both normal weight and overweight or obese adolescents, averaging roughly 12 grams per day, or 5 grams/1000 kcals (71). High intake of dietary fiber has also been shown to be significantly inversely associated with metabolic syndrome in a large sample of adolescents (72). This study suggested that encouraging a diet high in fiber might be more beneficial than restricting food choices that are high in fat or cholesterol only. Dietary quality is important for those in all weight categories and must be addressed for overall health across the board and not just a focus in those who are overweight or obese.

The lack of consistent patterns of dietary intake among those who are normal weight versus those who are overweight or obese, make creating overall conclusions regarding the role of diet, and from those conclusions recommendations, difficult. Fruit and vegetable consumption, in addition to fiber intake, have been shown to be beneficial regardless of weight status and it appears that there is an inverse association between the consumption of these foods and body weight (73). As more research is done examining differences in dietary intake between normal and overweight and obese children and adolescents, potential trends may start to emerge that can assist those working to combat the problem of obesity among the youth.

IV.B. Diet and CRP

In addition to investigating exercise training as a way to decrease vascular inflammation, diet needs to be examined as well. Kelishadi et al. (40) examined the effect of a lifestyle modification program that included both exercise and dietary changes on flow mediated dilation and CRP. The subjects (19 boys and 16 girls) participated in MVPA (30 minutes of fitness activities and 30 minutes of games/running) 60 minutes, three days a week, for six weeks. The subjects were also given dietary advice on a moderate diet designed to maximize the energy content based on the height of the child. Body weight, BMI, waist circumference, percent body fat, lipid measurements, and CRP all decreased after six weeks of training and dietary changes and flow-mediated dilation showed significant improvement. There was a reduction in subjects classified as having metabolic syndrome from 34.2% to 14.2% after the training program. This study incorporated less exercise training time than seen in other studies, but documented decreases in CRP. This may be due to the dietary changes made in conjunction with the exercise training program, which may have lead to the weight and body fat decreases. While functional endothelial changes have been shown to happen without changes in body mass or fat mass, this study highlights the importance of decreasing body mass and fat mass to facilitate the changes in vascular function, which are very important to address in addition to endothelial function.

Examining evidence from observational studies, Ford et al. (74) examined data from NHANES III (1988-1994) and observed an inverse relationship between the Healthy Eating Index (HEI) score and level of CRP. With further analysis, the relationship was attributed to one individual component, namely grain consumption. The authors postulated that grain consumption could influence the reduction of inflammation due to the specific nutrients often contained in whole grains, including linoleic acid, fiber, vitamin E, selenium, magnesium, and potassium.

Fiber intake has been shown to have an inverse relationship with CRP (75-77) and many studies have investigated fruit and vegetable intake, as they are high in both fiber and antioxidants (78-82). Gao et al. (81) reported that the prevalence of high CRP was significantly greater for those subjects in the lowest quintile for fruit and vegetable consumption, while Watzl (82) showed a significantly reduced level of CRP in subjects who consumed eight servings per day of fruits and vegetables compared to those who ate two servings per day in a cohort of male non-smokers. Esposito et al. (83) demonstrated that a high fat meal supplemented with vegetable antioxidants (tomatoes, peppers, and carrots) could reduce the extent of endothelial dysfunction that was measured after a high fat meal alone.

Omega-3 fatty acids have also been recognized as an anti-inflammatory nutrient, with both observational studies (84-87) and interventional studies (88-90) showing inverse relationships between the consumption of these fatty acids and the reduction of inflammatory markers, including CRP. Results from Pischon et al. (84) showed that those subjects who had the lowest levels of inflammatory markers were those who had the highest intake of both omega-3 fatty acids and omega-6 fatty acids, highlighting that the combination of the two may show the best benefit. Improved vasodilation of the brachial artery, measured by flow-mediated dilation, has also been documented with consumption of omega-3 fatty acids (91), as has vasodilation of the coronary arteries as measured by an infusion of intracoronary acetylcholine (92).

Different dietary patterns have been investigated as to their influence on markers of inflammation and endothelial function. A vegetarian diet low in trans fatty acids and saturated fat has been shown to lower levels of CRP (93), while a very low carbohydrate diet led to significant decreases in CRP (94). Additionally, a result from the Oxford Vegetarian Study showed that BMI values were higher, on average in non-vegetarians compared with male and female

vegetarians across all age groups (73). The lower BMI values in vegetarians may be a result of a higher consumption of high fiber, low energy fruits and vegetables compared to non-vegetarians. One of the most well-studied diets is the Mediterranean Diet, which is high in olive oil, nuts, vegetables, legumes, fruit, and fish, moderate in dairy and alcohol, and low in red meat and processed foods. This dietary pattern has been shown to reduce CRP levels (95, 96) and improve endothelial function (97, 98). One component of the Mediterranean Diet that has received considerable attention is alcohol consumption. Moderate consumption has been shown to lower CRP levels compared to non-drinkers and heavy drinkers (99-101). The addition of red wine to a high fat diet was shown to mediate a reduction in endothelial function that was seen in subjects consuming the high fat diet without the addition of red wine (102). The consumption of red wine and green olive oil (virgin olive oil) was also shown to produce significant improvements in endothelial function compared to white wine and regular olive oil (98). Nuts, a component of the Mediterranean Diet, have seen varied results when examining their ability to reduce levels of CRP. Two studies focused on consumption of nuts showed no significant improvement in CRP (103, 104), while a third saw a significant increase in CRP with intake of walnuts, but did not see any change in CRP with ingestion of cashews (105).

Overall, there are multiple dietary components that can be beneficial to preventing inflammation and endothelial dysfunction. A whole food approach to incorporating these nutrients and dietary patterns in a healthy lifestyle that aims to keep a healthy weight and accumulate adequate physical activity may lead to a more heart healthy life. More research is focusing on the dietary patterns of individuals and the intake of specific nutrients as a way to combat vascular inflammation, which has been shown to be paramount in the development of atherosclerosis. Additionally, specific foods and patterns of eating have emerged as pro-

inflammatory, which have been shown to increase levels of CRP and impair endothelial function. A balanced diet, heavy on anti-inflammatory foods and light on pro-inflammatory foods, with plenty of daily physical activity, may be the panacea to combat cardiovascular disease.

V. COMBINED ASSOCIATION OF FATNESS AND PHYSICAL ACTIVITY

The independent association between physical activity and fatness with measures of vascular health – blood pressure and CRP – are well documented, but little research has been performed focusing on the combined association of these two factors. With the current prevalence of overweight and obesity in children and adolescents, and the low prevalence of children and adolescents meeting the physical activity guidelines, it is clear that these two variables often occur in tandem. While the combination of low physical activity and high fatness is one that needs to be investigated, further examination of high physical activity combined with high fatness (fat-active) and even low physical activity and normal fatness should warrant attention as well.

The combined association of a similar construct, aerobic fitness, and fatness has been examined in both adults and children. Building on the work of Blair and colleagues in adults (106, 107), these studies in children and adolescents (108-111) clearly showed that aerobic fitness attenuated the influence of fatness on components of metabolic syndrome, including blood pressure. While aerobic fitness and physical activity have been shown to be moderately associated in children and adolescents (112, 113), they are different constructs. Specifically, aerobic fitness is a physiological and anatomical trait that integrates the cardiovascular and respiratory systems with oxidative properties of the skeletal muscles, whereas physical activity is a behavior defined as any bodily movement produced by skeletal muscles that results in an increase in energy expenditure over resting levels (114). Current public health guidelines for

both adults and children focus on physical activity, not aerobic fitness. Due to this focus on physical activity and the current prevalence of overweight and obesity, a clear understanding of the combined association of physical activity and fatness is necessary.

Parrett et al. (115) explored the combined association of physical activity and fatness on CRP in forty-five prepubescent children. Physical activity was measured by use of pedometer and fatness was determined by use of dual-energy x-ray absorptiometry and by calculation of BMI. The average number of steps taken over the four-day period was used as an estimate of physical activity. Subjects were categorized into high and low activity groups based on the median split of the number of steps taken per day. High fat and low fat groups were formed based on two classifications – age- and sex-specific BMI cut points and sex-specific cut points for percent body fat as measured by dual-energy x-ray absorptiometry. BMI and percent body fat were significantly correlated ($r=0.89$). Main effects for both fatness (BMI and percent body fat) and physical activity were found, but no significant interaction between the two. Additional analyses were conducted and physical activity as measured by pedometer accounted for 10% of the variance, with percent body fat accounting for 16%. While no combined association was found, the main effect of physical activity and the strong influence of fatness on CRP highlight the importance of encouraging children and adolescents, especially those who are overweight or obese, to be physically active. The small sample size of this study is a limitation that could be overcome with a larger, more diverse sample. A larger sample may shed light on the whether a combined association is present between physical activity and fatness.

Hayes et al. (116, 117) also examined the combined association of physical activity and fatness on blood pressure and CRP in two separate populations of children and adolescents. In the first study (116), physical activity was measured by acelerometry and percent fatness was

determined by dual-energy x-ray absorptiometry. Subject (mean age 7.7 ± 1.2 years) were divided into four groups based on cut points for meeting or not meeting the physical activity recommendations of 60 minutes of moderate-to-vigorous physical activity per day and for level of fatness based on the cut points from the FITNESSGRAM protocol. Physical activity did not significantly influence blood pressure within the fatness categories. Subsequently, the combined association of physical activity and fatness on blood pressure and CRP was examined in a second population of children and adolescents (mean age 10.5 ± 0.4 years). Physical activity was assessed by self-report and BMI was used as a proxy for measured fatness. Physical activity did not influence either blood pressure or CRP within fatness groups. As with the study by Parrett, sample size may have limited the results and the ability to quantify a combined association between physical activity and fatness. Additionally, a larger sample would allow for better classification based on the amount of physical activity accumulated throughout the day. Instead of only using meeting/not meeting the current physical activity recommendations as the cut point, minutes of physical activity (as measured by accelerometry) could be used and comparisons between low number of minutes, moderate number of minutes, and high number of minutes of physical activity could be used. The work of Parrett and Hayes have laid the foundation for further work to better answer the question as to whether there is a combined association of physical activity and fatness on blood pressure and CRP. Additional work should build upon the strengths of their studies (measurement, analysis), and address the limitations (sample size) to better understand how these two variable interact and possibly influence blood pressure and CRP in children and adolescents.

VI. SUMMARY AND CONCLUSION

The development of atherosclerosis in children and adolescents has been clearly shown through autopsy, clinical, and epidemiological studies in the past few decades. The influence of physical activity, diet, and adiposity on the early development of endothelial dysfunction has also been demonstrated in children and adolescents. As researchers move forward, we must better understand the complex combined association of physical activity, diet, and adiposity on CVD risk factors, especially in children and adolescents who are overweight and obese. Although the trend in obesity may be stabilizing, millions of children and adolescents are overweight and obese and have an increased risk of overweight and obesity as adults. In addition, adverse CVD risk factors are appearing earlier in life. By better understanding the influence of physical activity and diet in overweight and obese children and adolescents, more effective interventions can be developed to prevent and manage the risk factors that lead to cardiovascular disease.

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CHAPTER 2

PHYSICAL ACTIVITY, ADIPOSITY, AND VASCULAR HEALTH IN U.S. CHILDREN AND ADOLESCENTS: NHANES 2003-2006

INTRODUCTION

The development of atherosclerotic plaque as a precursor of cardiovascular disease (CVD) has been well established (1) and numerous autopsy studies (2-6) have shown that the development of atherosclerosis begins during childhood. In turn, events occurring early in the atherosclerotic process trigger disruptions in endothelial function. Endothelial function can be quantified by several methods. The main non-invasive direct method for quantifying endothelial function is flow-mediated dilation (7). Blood pressure (BP) and biomarkers, namely C-reactive protein (CRP), have been associated with endothelial dysfunction and are used clinically as markers of endothelial (dys)function (8, 9). Blood pressure is the most common of these markers of endothelial function, as it is routinely measured during medical visits. Clinically, elevated CRP is used as a marker/indicator of low-grade vascular inflammation, which occurs during the atherosclerotic process (10). Due to the clinical significance and prevalence of use, these two measures are the focus of this study.

High body fatness adversely influences blood pressure and vascular inflammation (11-16), leading to concern given the high prevalence of overweight and obesity among children and adolescents (17). Elevated blood pressure and impaired endothelial function (typically assessed via elevated CRP) (11, 15, 16, 18-20) are often identified together, especially in children and adolescents who are overweight or obese. In children and adults, high levels of CRP have been associated with high body mass index (BMI), visceral adiposity, insulin resistance, and

hypertension (16, 21, 22). The positive association between CVD risk factors and fatness is concerning as these risk factors can cluster (e.g., metabolic syndrome), and track moderately well from childhood and adolescence into adulthood (23).

Physical inactivity is recognized as an independent risk factor for cardiovascular disease and is associated with other risk factors for cardiovascular disease (24). Additionally, physical activity is inversely related to fatness in both children and adults (25). Several studies have shown univariate relationships between fatness and blood pressure and fatness and CRP (12, 16, 26). In general, there is a moderate, positive relationship between fatness and blood pressure and CRP (27-37). Additionally, several studies have reported a weak inverse relationship between physical activity and blood pressure (38). Fewer studies have examined the relationship between physical activity and CRP, and to date the results are mixed with studies showing no relationship (39, 40), a positive relationship (41), and an inverse relationship (28, 42, 43). Thus, associations among fatness, blood pressure, CRP, and physical activity are not clear but important due to their relevance to cardiovascular disease prevention.

Various factors, including age and gender, can influence blood pressure and CRP levels. Boys have been shown to have higher systolic blood pressure than girls (44) and blood pressure has been shown to increase with age (45). Age and gender differences in CRP levels have not been examined as extensively as they have been with blood pressure, but a trend for higher levels of CRP in women compared to men has been identified, with this difference appearing during the time of puberty (46). The positive relationship between CRP levels and age has been examined, and while there appears to be an age-related change in CRP levels, it has also been noted that the increase in visceral fat that often accompanies aging might be the primary cause of this increase in CRP (47). Examining the relationships of age and gender with blood pressure and CRP in

children and adolescents may assist in better understanding these relationships in adulthood and the effect they have on the overall risk of CVD.

Our previous work explored the combined association of physical activity with fatness on CVD risk factors, and showed a strong positive association between fatness and blood pressure in 5 to 9 year olds (48) and 9 to 12 year olds (49); this positive association was also evident between fatness and CRP in 9 to 12 year olds (49). An inverse relationship between physical activity and blood pressure and CRP was not evident. Additionally, there was no combined association between fatness and physical activity in either study, in part due to limitations including small sample size (n=91-174), a low percentage of obese subjects, and the use of self-reported physical activity. In the only additional study that examined this combined association between physical activity and fatness, Parrett et al. (43) found a main effect for both fatness and physical activity on CRP, but no interaction (i.e., combined association) in 9 year olds. Further study is warranted in larger samples, with a greater variance of weight status, and objective measures of physical activity. Given the relatively high prevalence of overweight and obesity (17), and low levels of physical activity in children and adolescents (50), understanding the combined association of fatness and physical activity could be beneficial in designing interventions and clinical programs that address these risk factors. Therefore, the purpose of the present study was to examine the independent and combined association (interaction) of physical activity and fatness on resting blood pressure and CRP in a nationally representative sample of United States (U.S.) children and adolescents 6 to 18 years. It was hypothesized that there would be a positive relationship between fatness and resting blood pressure, and fatness and CRP, and an inverse relationship between physical activity and resting blood pressure, and physical activity and CRP. It was also hypothesized that an interaction between fatness and physical

activity with blood pressure and CRP would be detected. Additionally, it was hypothesized that there would be sex differences with boys having higher resting blood pressure than girls and girls having higher CRP measurements than boys. This investigation builds on previous research due to use of a significantly larger sample size and use of objective assessment of physical activity.

METHODS

Study design. Cross-sectional data from the 2003-2004 and 2005-2006 National Health and Nutrition Examination Survey (NHANES) (51) were used in this secondary data analysis. NHANES is a surveillance system designed to assess the health and nutritional status of adults and children in the U.S. through a combination of interviews and physical examinations. NHANES collects data at 15 different geographic locations that are selected randomly annually. Participants are selected from these different geographic locations based on a complex sampling and weighting method allowing for a representative sample of the U.S. population. The survey protocols and procedures were approved by the National Center for Health Statistics ethics review board and all materials were produced in English and Spanish with bilingual staff conducting the surveys and health examinations. The analysis of this data from NHANES was not submitted to the Michigan State University Institutional Review Board for approval, as it did not meet the criteria for involving human subjects since the data were de-identified for all analyses.

Subjects. Children and adolescents 8 to 18 years of age with complete data on BMI, blood pressure, CRP, and physical activity were included in the analyses. Physical activity data were included if subjects had a minimum of four days of physical activity measurement with a minimum wear time of the accelerometer of 10 hours per day (52). Children with a CRP level

greater than 10.0 mg/L, those missing key variables, children and adolescents with a BMI of less than the 5th percentile, and pregnant girls were excluded. A CRP level greater than 10.0 mg/L has been shown to be associated with a current infection or illness and not a true measure of inflammation. Subjects with a BMI less than the 5th percentile are classified as underweight, and because the purpose of this study is to examine the combined association of fatness and physical activity, it was determined that those who were underweight would be excluded. Pregnancy can influence physical activity levels and BMI, therefore pregnant girls were also excluded. A total of 2,585 (1303 males, 1282 females) 8-18 year olds (47% of total 8-18 year olds) met these criteria. The reduced number of subjects meeting the inclusion criteria was due to a low number of subjects with complete physical activity data. Standard NHANES procedures are explained in the following text.

Blood Pressure. Blood pressure was measured by a physician during the physical examination in accordance with the American Heart Association protocol (53). Appropriately sized pediatric cuffs were used. Per the American Heart Association protocol, Phase IV Korotkoff sounds were used to determine diastolic blood pressure in children under the age of 13 years. While three measures were attempted, in some cases, participants only had one or two valid blood pressure measures. When multiple blood pressure readings were available, they were averaged for analysis. Mean arterial pressure (MAP) was calculated as follows: $MAP = .66(\text{Diastolic Blood Pressure}) + .33(\text{Systolic Blood Pressure})$.

High Sensitivity C-Reactive Protein (CRP). Participants had venipunctures completed by a certified phlebotomist. Participants were asked about recent illness and infections prior to the blood draw. Blood was drawn from the median cubital vein. The following volumes were drawn

for the different age ranges of participants: 6-11 years – 35 mL and 12+ years – 104 mL. Once the blood was drawn and processed in the mobile examination center, it was stored and shipped to the University of Washington Medical Center, Department of Laboratory Medicine, Immunology Division for analysis. Samples were processed using a Dade Behring Nephelometer II Analyzer System (Dade Behring Diagnostics Inc., Somerville, NJ). Calibration and control procedures were in place using a standard that was prepared by the manufacturer and standardized against the World Health Organization International Reference Preparation of CRP (54). Log-transformed CRP values were used in the analysis due to a non-normal distribution.

Anthropometry. Participants' weights were measured on a digital scale (Toledo Scale, Columbus, OH) in pounds and converted to kilograms and height was measured on an electronic stadiometer (Seca Ltd, Medical Scales and Measurement Systems, Birmingham, United Kingdom) to the nearest millimeter. BMI (kg/m^2) was calculated and BMI percentiles were determined from the Centers for Disease Control and Prevention SAS growth chart computer program (http://www.cdc.gov/growthcharts/computer_programs.htm). BMI was used as a proxy for fatness since BMI is widely used clinically and epidemiologically to categorize children as overweight or obese (55).

Physical Activity. Participants were asked to wear an Actigraph accelerometer (model 7164, Actigraph, LLC; Ft. Walton Beach, FL) for the seven days after their medical examination. Participants wore the accelerometer during waking hours on their right hip on an elastic belt and were asked to remove it only when swimming or bathing. At the end of the seven days, participants returned the accelerometers via express mail. At that time, the data were downloaded and the accelerometers checked to determine whether the device was still working within the manufacturer's calibration specifications. The accelerometer recorded counts (vertical

acceleration) in one-minute epochs for up to one week. The amount of time participants spent in moderate- to vigorous-physical activity (MVPA) was calculated based on count thresholds that correspond to MVPA (56). These thresholds were devised based on calibration studies examining the relationship between accelerometers and measured energy expenditure. For children and adolescents, age-specific criteria was used for the following thresholds: 4 metabolic equivalents (METs) for moderate activity and 7 METs for vigorous activity to account for a greater overall energy expenditure in children and adolescents (56). For inclusion in the analyses, subjects needed a minimum of four days of physical activity measurement with a minimum wear time of the accelerometer of 10 hours per day (52).

DATA ANALYSIS

Descriptive characteristics were calculated for the total sample and by sex accounting for the complex survey design and weighting. Sex differences were examined by t-test. Fatness was categorized based on age- and sex-specific BMI percentiles: normal weight ($\geq 5^{\text{th}}$ < 85^{th} percentile), overweight ($\geq 85^{\text{th}}$ percentile < 95^{th} percentile), and obese ($\geq 95^{\text{th}}$ percentile), and physical activity was categorized based on the participants' minutes of MVPA per day: least active (<15 minutes MVPA/day), low active (≥ 15 -59 minutes MVPA/day), and active (≥ 60 minutes MVPA/day). The cut point for the active group is based on the current national physical activity guidelines (57). To examine main effects and the combined association (interaction) between physical activity and fatness on blood pressure and CRP, multiple linear regression analysis was used examining the main effects of fatness and physical activity and the interaction of fatness and physical activity. Sex-specific analyses were conducted with age and race used as covariates. CRP was log-transformed. Blood pressure was analyzed separately as SBP, DBP, and

MAP. The normal weight group, the active group (≥ 60 minutes per day), females, and Caucasians were used as the referent groups in the models. In the interaction models, the referent group was normal weight/active (≥ 60 minutes per day). All statistical analyses including multiple-linear regression models were performed using SUDAAN Version 10.0.1 (RTI, International, Research Triangle Park, NC), with the level of significance set at an Alpha level of $p < 0.05$. The complex sample design, including sample weights, clusters, and stratification variables, was accounted for in all analyses using standard methods (51). Due to the oversampling of 12 to 18 year olds, analyses by age category (i.e., 8 to 11 year olds and 12 to 18 year olds) were not conducted as the two groups would be not be well matched in number of participants in each age group.

RESULTS

Descriptive characteristics of the sample ($n=2585$) are shown in Table 1. The distributions of fatness and BMI by age are presented in Figures 1 and 2, and the distributions of SBP (Figure 3), DBP (Figure 4), and MAP (Figure 5) are also presented. These distributions represent raw, un-weighted data and are presented to provide an overall view of the trend of each main factor in relation to the age of the sample. Lines of best fit (Loess method) are included for each distribution. The sample was predominantly Caucasian (61.9%), African American (14.7%), and Mexican American (12.1%), with the remaining population classified as other Hispanic (4.9%) or other (6.3%). The mean age of the total sample was 13.5 ± 0.1 years. Overall, boys were significantly taller (159.8 ± 0.7 cm vs. 154.4 ± 0.5 cm; $p < 0.001$) and heavier than girls (57.0 ± 0.9 cm vs. 53.8 ± 0.8 cm; $p = 0.003$), though girls had a significantly higher BMI (21.6 ± 0.2 vs. 22.1 ± 0.3 ; $p = 0.033$). The BMI percentile for the total sample approximated the 65th percentile

with about 35% classified as overweight (18.3%) or obese (16.6%). Boys had significantly higher SBP [(108.2 mmHg $\pm$ 0.40 vs. 104.7 mmHg $\pm$ 0.61, respectively; ($p<0.0001$)] and significantly lower DBP (56.9 mmHg $\pm$ 0.58 vs. 58.7 mmHg $\pm$ 0.52, respectively; ($p=0.006$)) than girls. There were no significant sex differences in MAP or CRP. While CRP values were log-transformed for analysis due to non-normal distribution of values, the mean CRP values were less than 1.0 and thus considered normal.

Of the total sample, approximately 22% achieved less than 15 minutes of MVPA per day, 51% achieved between 15 and 59 minutes per day, and 27% exceeded 60 minutes per day. Boys spent substantially more time in MVPA compared to girls (54.4 $\pm$ 2.4 minutes/day vs. 35.2 $\pm$ 1.4 minutes/day, respectively; ($p<0.0001$)). When grouped into MVPA categories (least active, low active, and active), more girls were categorized as least active (<15 minutes of MVPA per day) than boys (30.3% vs. 13.2%, respectively), while a greater percentage of boys met the physical activity guidelines ($\geq$ 60 minutes of MVPA per day) than girls (35.0% vs. 19.7%, respectively) ($p<0.0001$). The mean wear time for the accelerometer was 14.1 hours per day, with boys accumulating slightly more wear time per day than girls (14.2 hours vs. 13.9 hours per day, $p<0.002$; Table 2).

Main effects for fatness were seen for SBP in the total sample ($\beta=8.03$), boys ($\beta=9.37$), and girls ($\beta=5.24$) (Table 3), MAP in the total sample ($\beta=3.71$) and girls ($\beta=4.73$) (Table 5), and CRP in the total sample ($\beta=1.68$), boys ($\beta=1.85$), and girls ($\beta=1.36$) (Table 6). Main effects for physical activity were seen for DBP in the total sample ($\beta=3.80$) and girls ($\beta=4.68$) (Table 4), MAP in the total sample ($\beta=2.58$) and girls ($\beta=3.18$) (Table 5), and CRP in girls ($\beta=-0.38$) (Table 6). A statistically significant combined association (interaction) was identified between fatness and physical activity for SBP in the total sample (Wald $F=204.60$; $p=0.0000$), boys

(Wald $F=85.85$; $p=0.0000$), and girls (Wald $F=89.14$; $p=0.0000$), for DBP in the total sample (Wald $F=18.68$; $p=0.0167$), and girls (Wald $F=17.90$; $p=0.0220$), for MAP in the total sample (Wald $F=36.32$; $p=0.0000$), and girls (Wald $F=28.08$; $p=0.0005$), and for CRP in the total sample (Wald $F=606.30$; $p=0.0000$), boys (Wald $F=283.57$; $p=0.0000$), and girls (Wald $F=327.75$; $p=0.0000$) (Table 7). When examining group differences (least-square means) in the total sample in SBP (Figure 6), a significant difference of 6mmHg was seen in those in the obese/least active (<15 minutes/day) group compared to the normal weight/active group, while the largest difference (8 mmHg) was between the obese/active group and the normal weight/active group. The overweight/least active group had a significant difference of 4mmHg with the normal weight/active group. Similar significant differences were seen when analyzing DBP (Figure 7) and MAP (Figure 8), with both the overweight/least active group and the normal weight/least active group demonstrating a 4mmHg difference in DBP compared to the normal weight/active group, while the obese/less active (15-59 minutes/day) group, the obese/active group, and the overweight/least active group had a 4mmHg difference in MAP with the normal weight/active group.

Age was significant ($p<0.01$) in the model for each analysis except CRP in boys ($p=0.0756$). Sex was significant in the model for SBP in the total sample ($\beta=3.70$; $p=0.0000$) and DBP in the total sample ($\beta=-1.32$; $p=0.0270$) only. Race was significant in the analysis for DBP in girls (other Hispanic; $\beta=-4.47$; $p=0.0487$), MAP in girls (other Hispanic; $\beta=-2.95$; $p=0.0341$), CRP in the total sample (Mexican American; $\beta=0.24$; $p=0.0003$), boys (Mexican American; $\beta=0.25$; $p=0.0130$), and girls (Mexican American; $\beta=0.24$; $p=0.0108$).

DISCUSSION

The main purpose of this study was to examine the independent and combined associations (interaction) of physical activity and fatness on resting blood pressure and CRP in a nationally representative sample of U.S. children and adolescents. Additionally, gender differences related to both blood pressure and CRP were examined. The main findings of this study include the following: a positive relationship between fatness and resting blood pressure and CRP, an inverse relationship between physical activity and resting blood pressure and CRP, and an interaction between fatness and physical activity with blood pressure and CRP; all supporting the hypotheses of this study. Additionally, the results supported the hypothesis that boys would have higher resting blood pressure than girls. The results did not support the hypothesis that girls would have higher CRP measurements than boys. To our knowledge, this study is novel in that the association between fatness and physical activity with blood pressure and CRP has not been examined in a large sample of children and adolescents using an objective measure of physical activity. Our findings add to the literature in the area of physical activity and CVD risk factors in children and adolescents.

Previous studies have shown a positive relationship between fatness and blood pressure (29, 58-60). Additionally, in studies of both children and adults, a high level of CRP has been shown to be associated with increased BMI, visceral adiposity, insulin resistance, endothelial dysfunction and hypertension (16, 21, 22). In concordance with these previous studies, a main effect for fatness was seen for SBP in the total sample, boys and girls, for MAP in the total sample and in girls, and for CRP in the total sample, boys, and girls. No main effect was seen in any analysis for DBP or for MAP in boys. DBP can be difficult to measure reliably in children and adolescents due to difficulty detecting Korotkoff sound IV, which may explain the lack of

results compared to SBP (61). These results highlight the importance of addressing reductions in fatness in children as young as 8 years old. An increase in vascular inflammation and blood pressure, due to an increase in fatness, can set the stage for a clustering of CVD risk factors in childhood, which can then track into adulthood. Identifying children and adolescents with early, easily measureable CVD risk factors can allow for treatment to begin before more advanced disease progression occurs.

A main effect for physical activity was evident in the total sample for both DBP and MAP, but not SBP. This might have been influenced by the girls in the sample, as there was a main effect seen in both DBP and MAP for girls, but not boys. These results are similar to those found in the literature, which has shown that physical activity is beneficial to reducing numerous cardiovascular risk factors, including blood pressure (25, 30, 62). Regarding CRP, the only main effect for physical activity was seen in girls, but not in boys or the total sample. Physical activity, both objectively measured by accelerometers and measured by self-report, has been shown to be significantly associated with CRP, even after adjusting for BMI, in adults measured in the 2003-2004 and 2005-2006 NHANES surveys (63). Parrett et al. also reported a main effect of physical activity on CRP in a small sample (n=45) of prepubescent children (mean age 9.4 years), though due to the sample size, no sex-specific analysis was conducted. While physical activity was not as consistently related to CRP, more research is needed to better understand how a child's level of physical activity can influence CRP. As more pediatric research includes CRP as an outcome, these questions will begin to be answered more completely.

A combined association (interaction) between fatness and physical activity was evident in all analyses of blood pressure and CRP except MAP and DBP in boys. These are novel findings, as this association has not been studied widely in relation to either blood pressure or CRP.

Additionally, we found no previous studies that indicated significant interactions. Parrett et al. (43) found that physical activity determined by pedometer steps per day explained 10% of the variance when examining the combined association of fatness and physical activity in a cohort of 9 year olds, but no significant interaction between fatness and physical activity was found. Hayes et al. also examined this combined association in two different samples of children and adolescents, again, finding no interaction (48, 49). These previous studies used a combination of subjective and objective measures of both fatness and physical activity, but the major limitation of both was overall sample size. The current study used an objective measure of physical activity in a sample of significant size. While use of a more sophisticated measure of fatness was desired, the wide spread use of BMI in both large epidemiological studies and clinical environments justified the use in this analysis. The combined association of fatness and physical activity observed in this representative sample highlight the importance of both fatness and physical activity when addressing CVD risk factors in children and adolescents. The priority in public health should be on reducing overall fatness and increasing daily physical activity as these results show that they interact in relation to blood pressure and CRP.

The current findings are both statistically and clinically significant. Differences in SBP, DBP, and MAP ranged from 4-6 mmHg between groups. A 5mmHg reduction in blood pressure has been shown to decrease mortality due to coronary heart disease, cardiovascular disease, and all cause mortality by 10.5%, 11.3%, and 7.9% respectively (64). Similarly, there was a significant difference among groups when examining CRP. All three obese and overweight groups had significantly different CRP measurements compared to the normal weight/active group. Less is known about clinically significant differences in CRP in children than is known regarding clinical significance in blood pressure, but the clear effect of fatness on CRP

measurement makes a strong statement regarding the influence of overweight and obesity on the cardiovascular health of children and adolescents.

There are clear gender differences in hypertension and CVD events (i.e., myocardial infarction, stroke) with an earlier occurrence in men and an increase in the rate for women after menopause. It is unclear when these gender differences begin. In this sample, boys had a significantly higher mean SBP (4mmHg) than girls, while they had a significantly lower (2mmHg) DBP than girls. Since there was no measure of maturation to differentiate between children and adolescents, it is difficult to definitively state that the difference is solely based on gender. It could be the result of predominantly more mature boys than girls in the sample. Future work on examining the gender differences with blood pressure in children and adolescents need to take maturation into account to better answer this question. Additionally, race was significant in the models for DBP and MAP with girls only and all three analyses (total sample, boys, and girls) for CRP. Racial differences in the prevalence of CVD risk factors, including hypertension and CRP, have been shown in studies with adults (65, 66) and children (67, 68).

The overall prevalence of children and adolescents classified as overweight (18.3%) and obese (16.6%) is of concern due to its association with the development of atherosclerosis (69), elevated blood pressure (60), and elevated CRP (31). As physical activity is often used as a means to regulate weight status, the low prevalence of boys (35.0%) and girls (19.7%) meeting the current recommendation of 60 minutes of MVPA per day is also a serious public health issue. While the overall prevalence of low physical activity is concerning, the prevalence of fat-active children and adolescents – 25% of obese boys classified as active and 10% of obese girls classified as active – shows that there are obese children and adolescents who meet the physical activity guidelines. In addition to exploring fat-active children and adolescents, it is also

important to understand whether normal weight children and adolescents are meeting the physical activity recommendations. In this study, only 20% of the total sample was classified as normal weight/active. Clearly, interventions focused on increasing physical activity levels need to focus on all children and adolescents and not solely on those who are overweight or obese. Physical activity levels decline from childhood to adolescence (50), and the prevalence of adults meeting the current physical activity recommendations is roughly 22% (70). Encouraging adequate levels of physical activity needs to be a priority in all children, adolescents, and adults, regardless of their fatness level or weight status.

Many environmental and genetic factors work in conjunction to affect health status, leading to a greater need for studies of combined associations to gain a clearer picture on how these factors work to influence biological functions such as blood pressure and CRP. The heritability of blood pressure has been shown to be 30-50%, with environmental influences reaching up to 50% (71) and CRP shows a similar estimated heritability (35-40%) (72). Future studies should account for family history, including family history of CVD risk factors, maternal health during pregnancy, and birth outcomes, as it has been shown that there is a genetic component to both blood pressure and CRP.

In addition to the genetic factors noted above, several environmental factors influence blood pressure and CRP. Besides physical activity, which was assessed in the current study, diet has been shown to play an important role in treatment of both elevated blood pressure and CRP. Diet was not investigated in this study as the subsample who had dietary data would have reduced the overall sample size dramatically. Grain consumption, namely the components of whole grains such as linoleic acid, fiber, vitamin E, selenium, and magnesium, has been shown to have a beneficial relationship in reducing CRP (73). Fiber intake is inversely related to CRP

(74, 75) and many studies have investigated fruit and vegetable intake since they are high in both fiber and antioxidants and low in saturated fat, which are also beneficial to healthy blood pressure (76-80). A diet rich in fruits, vegetables, and key micronutrients (potassium, calcium, and magnesium) and low fat dairy has been shown to be effective in improving elevated SBP (81). Sleep and screen time (television, computer, and video games) have also been shown to be environmental determinates to childhood obesity (82, 83). Future studies need to incorporate a variety of both environmental and genetic factors into such models to better understand the determinants that are exerting an influence on blood pressure and CRP in children and adolescents.

A major strength of this study was the use of a nationally representative sample of children and adolescents (i.e., NHANES). While NHANES is cross-sectional, the sample size allowed for the investigation of gender differences and the influence on the combined association of physical activity and fatness. However, this study was limited in that many potential environmental and genetic factors that influence the associations were not included in the models due to the sampling protocol of NHANES. Including data on some of the environmental factors would have decreased the sample size, thereby decreasing the ability to examine the combined association in a large, nationally representative sample. Lastly, the use of BMI in place of an objective measure of fatness may be seen by some as a limitation of this study. However, the use of BMI in clinical and public health settings has been shown to be appropriate in children and adolescents (84).

CONCLUSION

The findings of this study have shown the combined association (interaction) of fatness and physical activity on blood pressure and CRP in a nationally representative sample of U.S. children and adolescents and add a novel component to the literature. Given the current prevalence of overweight and obesity in children and adolescents, more focus is needed on preventing excess weight gain, as the association between fatness and CVD risk factors is strong. The low percentage of children and adolescents meeting recommendations for daily physical activity is a public health concern and interventions focused on the school, the home, and the community must be a priority to encourage greater levels of physical activity. This study has shown that these two factors (fatness and physical activity) interact in regard to two markers of vascular health in children and adolescents – blood pressure and CRP. Future research should address some of the prominent environmental (diet) and genetic (maternal history) aspects that could also influence this relationship.

APPENDIX

APPENDIX

Table 1. Descriptive characteristics of the sample. Values are mean (SEM) or percentage in specific category.

	Boys (n=1303)	Girls (n=1282)	Total (n=2585)
Age	13.5 (0.1)	13.5 (0.1)	13.5 (0.1)
Height (cm)	159.8 (0.7)*	154.4 (0.5)	157.2 (0.5)
Weight (kg)	57.0 (0.9)*	53.8 (0.8)	55.4 (0.7)
BMI (kg/m²)	21.6 (0.2)*	22.1 (0.3)	21.9 (0.2)
BMI Percentile	64.7 (1.1)	65.9 (1.3)	65.3 (1.0)
<i>Normal Weight</i>	65.5%	64.7%	65.1%
<i>Overweight</i>	18.6%	18.0%	18.3%
<i>Obese</i>	16.0%	17.4%	16.6%
Systolic Blood Pressure (mmHg)	108.2 (0.4)*	104.7 (0.6)	106.5 (0.4)
Diastolic Blood Pressure (mmHg)	56.9 (0.6)*	58.7 (0.5)	57.8 (0.5)
Mean Arterial Pressure (mmHg)	74.0 (0.4)	74.0 (0.5)	74.0 (0.4)
Log CRP	-3.14 (0.05)	-3.04 (0.06)	-3.09 (0.03)
CRP (mg/L)	0.13 (0.01)	0.16 (0.02)	0.15 (0.01)
MVPA (min)	54.4 (2.4)*	35.2 (1.4)	45.0 (1.6)
<i><15 minutes</i>	13.2%*	30.3%	21.6%
<i>15-59.9 minutes</i>	51.8%	50.0%	50.9%
<i>>60 minutes</i>	35.0%*	19.7%	27.5%

Sex differences analyzed by t-test accounting for complex sampling design. *Significant sex

difference $p < 0.05$; Normal Weight ($\geq 5^{\text{th}}$ BMI percentile $< 85^{\text{th}}$ BMI percentile), Overweight

($\geq 85^{\text{th}}$ BMI percentile $< 95^{\text{th}}$ BMI percentile), and Obese ($\geq 95^{\text{th}}$ BMI percentile)

Table 2. Duration of physical activity and use of accelerometer. Values are mean (SEM).

	Boys (n=1303)	Girls (n=1282)	Total (n=2585)
Minutes of Moderate Intensity PA	45.7 (1.8)*	30.5 (1.1)	38.3 (1.3)
Minutes of Vigorous Intensity PA	8.7 (1.0)*	4.7 (0.3)	6.8 (0.5)
Minutes of MVPA	54.4 (2.4)*	35.2 (1.4)	45.0 (1.6)
Mean Wear Time (hours)	14.2 (0.1)*	13.9 (0.1)	14.1 (0.1)

Sex differences analyzed by t-test accounting for complex sampling design. *Significant sex difference $p < 0.05$

Table 3. Independent relationship of fatness and physical activity on systolic blood pressure in the total sample, boys, and girls. (Multivariable linear regression model results)

	Beta Coefficient	Lower 95% Limit	Upper 95% Limit	P-Value
TOTAL SAMPLE				
Fatness				
<i>Obese</i>	8.03	5.34	10.72	<0.0001
<i>Overweight</i>	2.02	-0.34	4.38	0.0903
<i>Normal*</i>	0.00	0.00	0.00	-
Physical Activity				
<i>Least Active (<15 minutes)</i>	0.13	-2.50	2.76	0.9212
<i>Low Active (15-59 minutes)</i>	-0.31	-1.95	1.33	0.7034
<i>Active* (>60 minutes)</i>	0.00	0.00	0.00	-
BOYS				
Fatness				
<i>Obese</i>	9.37	5.87	12.86	<0.0001
<i>Overweight</i>	2.62	-0.26	5.49	0.0727
<i>Normal*</i>	0.00	0.00	0.00	-
Physical Activity				
<i>Least Active (<15 minutes)</i>	0.65	-1.58	2.88	0.5584
<i>Low Active (15-59 minutes)</i>	-0.03	-1.83	1.77	0.9737
<i>Active* (>60 minutes)</i>	0.00	0.00	0.00	-
GIRLS				
Fatness				
<i>Obese</i>	5.24	0.45	10.04	0.0332
<i>Overweight</i>	0.61	-3.90	5.12	0.7834
<i>Normal*</i>	0.00	0.00	0.00	-
Physical Activity				
<i>Least Active (<15 minutes)</i>	0.17	-3.49	3.83	0.9270
<i>Low Active (15-59 minutes)</i>	-1.13	-3.57	1.31	0.3512
<i>Active* (>60 minutes)</i>	0.00	0.00	0.00	-

*Referent Group

Table 4. Independent relationships of fatness and physical activity on diastolic blood pressure in the total sample, boys, and girls. (Multivariable linear regression model results)

	Beta Coefficient	Lower 95% Limit	Upper 95% Limit	P-Value
TOTAL SAMPLE				
Fatness				
<i>Obese</i>	1.55	-2.39	5.50	0.4281
<i>Overweight</i>	-0.00	-2.82	2.82	1.0000
<i>Normal*</i>	0.00	0.00	0.00	-
Physical Activity				
<i>Least Active (<15 minutes)</i>	3.80	0.94	6.67	0.0110
<i>Low Active (15-59 minutes)</i>	1.59	-0.60	3.78	0.1491
<i>Active* (>60 minutes)</i>	0.00	0.00	0.00	-
BOYS				
Fatness				
<i>Obese</i>	-0.01	-5.49	5.46	0.9957
<i>Overweight</i>	0.33	-2.84	3.50	0.8335
<i>Normal*</i>	0.00	0.00	0.00	-
Physical Activity				
<i>Least Active (<15 minutes)</i>	3.13	-1.46	7.73	0.1740
<i>Low Active (15-59 minutes)</i>	1.45	-1.74	4.64	0.3607
<i>Active* (>60 minutes)</i>	0.00	0.00	0.00	-
GIRLS				
Fatness				
<i>Obese</i>	4.47	-1.56	10.50	0.1402
<i>Overweight</i>	-0.61	-5.46	4.24	0.7990
<i>Normal*</i>	0.00	0.00	0.00	-
Physical Activity				
<i>Least Active (<15 minutes)</i>	4.68	1.15	8.21	0.0111
<i>Low Active (15-59 minutes)</i>	2.04	-1.33	5.40	0.2262
<i>Active* (>60 minutes)</i>	0.00	0.00	0.00	-

*Referent Group

Table 5. Independent relationships of fatness and physical activity on mean arterial pressure (MAP) in the total sample, boys, and girls. (Multivariable linear regression model results)

	Beta Coefficient	Lower 95% Limit	Upper 95% Limit	P-Value
TOTAL SAMPLE				
Fatness				
<i>Obese</i>	3.71	1.02	6.40	0.0085
<i>Overweight</i>	0.67	-1.61	2.96	0.5523
<i>Normal*</i>	0.00	0.00	0.00	-
Physical Activity				
<i>Least Active (<15 minutes)</i>	2.58	0.48	4.68	0.0177
<i>Low Active (15-59 minutes)</i>	0.96	-0.62	2.53	0.2250
<i>Active* (>60 minutes)</i>	0.00	0.00	0.00	-
BOYS				
Fatness				
<i>Obese</i>	3.11	-0.95	7.17	0.1277
<i>Overweight</i>	1.09	-1.36	3.54	0.3702
<i>Normal*</i>	0.00	0.00	0.00	-
Physical Activity				
<i>Least Active (<15 minutes)</i>	2.30	-0.84	5.45	0.1451
<i>Low Active (15-59 minutes)</i>	0.96	-1.36	3.28	0.4055
<i>Active* (>60 minutes)</i>	0.00	0.00	0.00	-
GIRLS				
Fatness				
<i>Obese</i>	4.73	0.13	9.33	0.0444
<i>Overweight</i>	-0.20	-4.60	4.20	0.9257
<i>Normal*</i>	0.00	0.00	0.00	-
Physical Activity				
<i>Least Active (<15 minutes)</i>	3.18	0.71	5.64	0.0133
<i>Low Active (15-59 minutes)</i>	0.98	-1.50	3.46	0.4258
<i>Active* (>60 minutes)</i>	0.00	0.00	0.00	-

*Referent Group

Table 6. Independent relationships of fatness and physical activity on CRP in the total sample, boys, and girls. (Multivariable linear regression model results)

	Beta Coefficient	Lower 95% Limit	Upper 95% Limit	P-Value
TOTAL SAMPLE				
Fatness				
<i>Obese</i>	1.68	1.35	2.01	<0.0001
<i>Overweight</i>	0.85	0.47	1.22	<0.0001
<i>Normal*</i>	0.00	0.00	0.00	-
Physical Activity				
<i>Least Active (<15 minutes)</i>	-0.12	-0.45	0.21	0.4623
<i>Low Active (15-59 minutes)</i>	0.02	-0.18	0.22	0.8094
<i>Active* (>60 minutes)</i>	0.00	0.00	0.00	-
BOYS				
Fatness				
<i>Obese</i>	1.85	1.43	2.26	<0.0001
<i>Overweight</i>	0.90	0.43	1.38	0.0006
<i>Normal*</i>	0.00	0.00	0.00	-
Physical Activity				
<i>Least Active (<15 minutes)</i>	0.16	-0.34	0.65	0.5215
<i>Low Active (15-59 minutes)</i>	0.09	-0.21	0.39	0.5301
<i>Active* (>60 minutes)</i>	0.00	0.00	0.00	-
GIRLS				
Fatness				
<i>Obese</i>	1.36	0.92	1.80	<0.0001
<i>Overweight</i>	0.70	0.13	1.27	0.0173
<i>Normal*</i>	0.00	0.00	0.00	-
Physical Activity				
<i>Least Active (<15 minutes)</i>	-0.38	-0.75	-0.01	0.0456
<i>Low Active (15-59 minutes)</i>	-0.13	-0.45	0.19	0.4295
<i>Active* (>60 minutes)</i>	0.00	0.00	0.00	-

*Referent Group

Table 7. Statistical significance of interactions between fatness and physical activity with systolic blood pressure, diastolic blood pressure, mean arterial pressure, and CRP in the total sample, boys, and girls.

	Degrees of Freedom	Wald F-Value	P-Value
Systolic Blood Pressure			
<i>Total</i>			
<i>Boys</i>	8	204.60	<0.0001
<i>Girls</i>	8	85.85	<0.0001
	8	89.14	<0.0001
Diastolic Blood Pressure			
<i>Total</i>			
<i>Boys</i>	8	18.68	0.0167
<i>Girls</i>	8	4.18	0.8405
	8	17.90	0.0220
Mean Arterial Pressure			
<i>Total</i>			
<i>Boys</i>	8	36.32	<0.0001
<i>Girls</i>	8	13.84	0.0859
	8	28.08	0.0005
CRP			
<i>Total</i>	8	606.30	<0.0001
<i>Boys</i>	8	283.57	<0.0001
<i>Girls</i>	8	327.75	<0.0001

Figure 1. Distribution of fatness by age in the total sample. Line of best fit (Loess method) is included. For interpretation of the references to color in this and all other figures, the reader is referred to the electronic version of this dissertation.

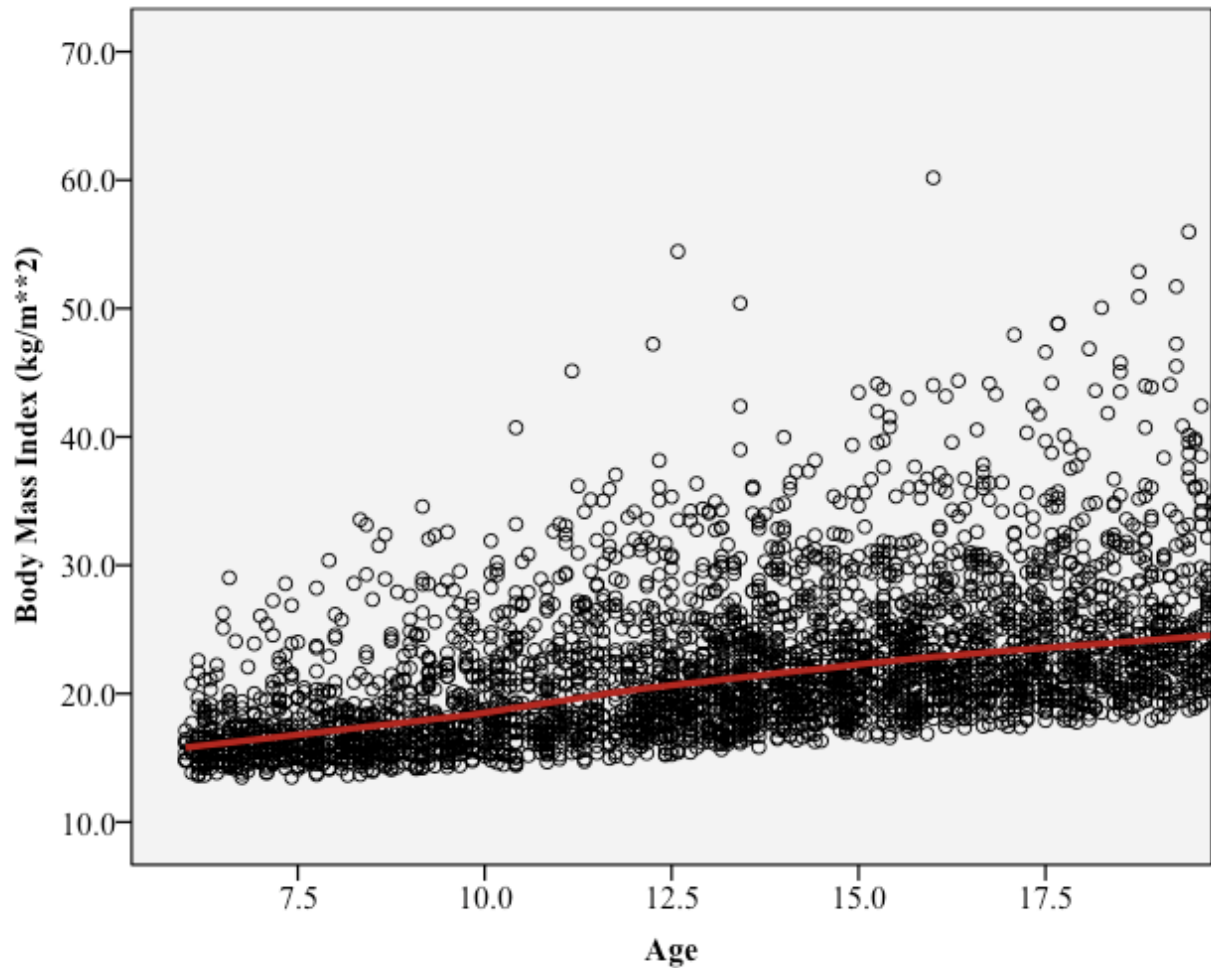


Figure 2. Distribution of moderate-to-vigorous physical activity by age in the total sample. Line of best fit (Loess method) is included.

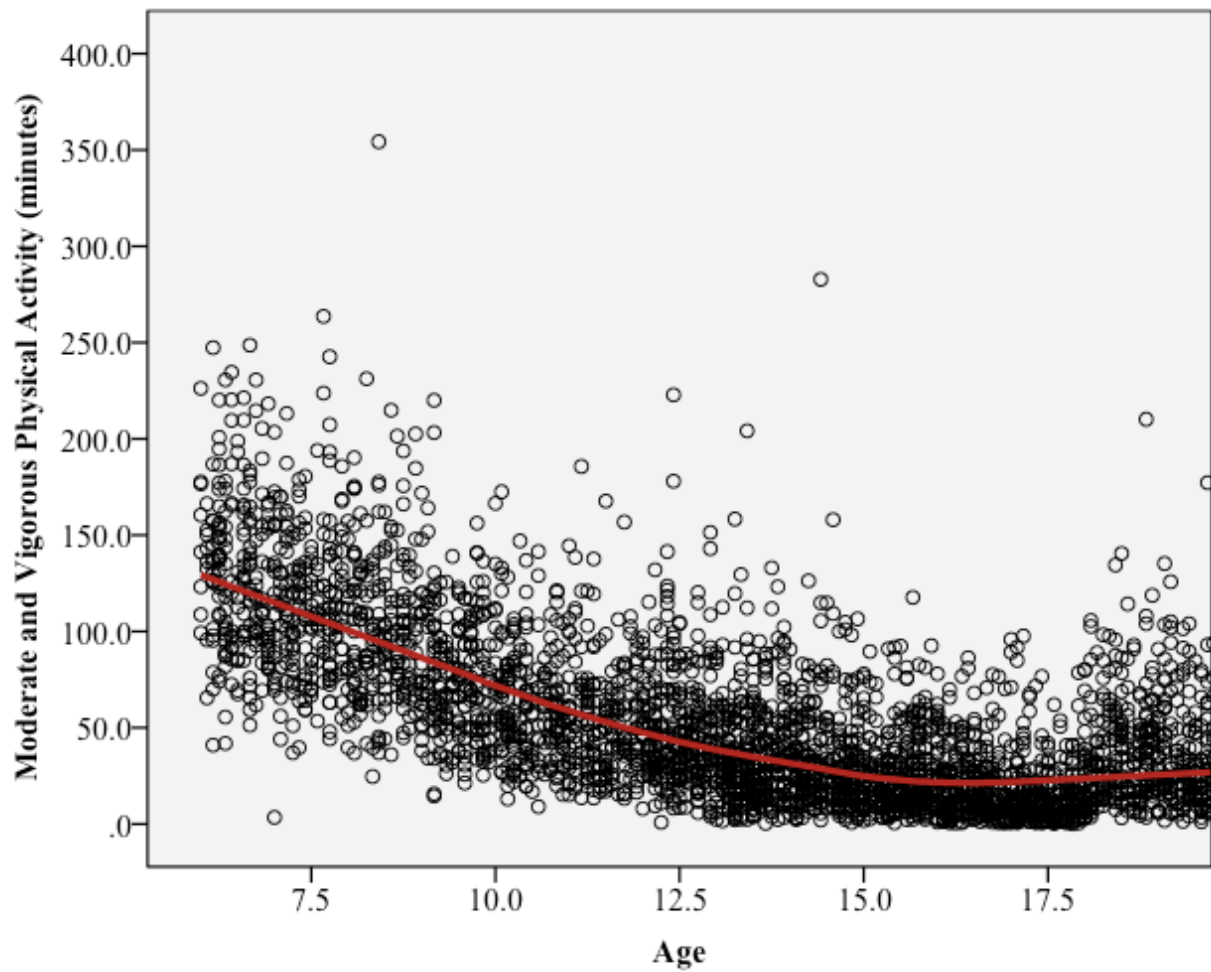


Figure 3. Distribution of systolic blood pressure by age in the total sample. Line of best fit (Loess method) is included.

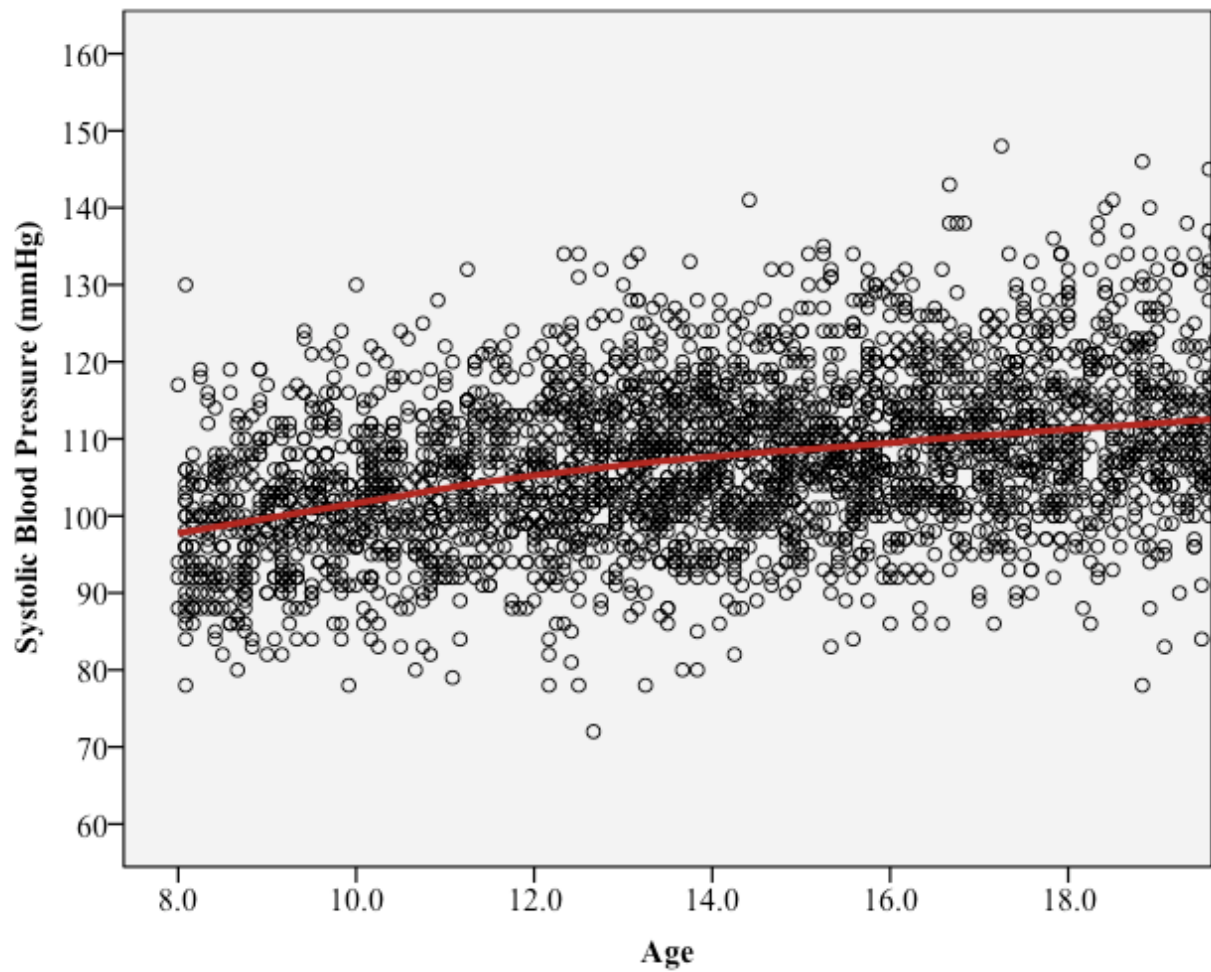


Figure 4. Distribution of diastolic blood pressure by age in the total sample. Line of best fit (Loess method) is included.

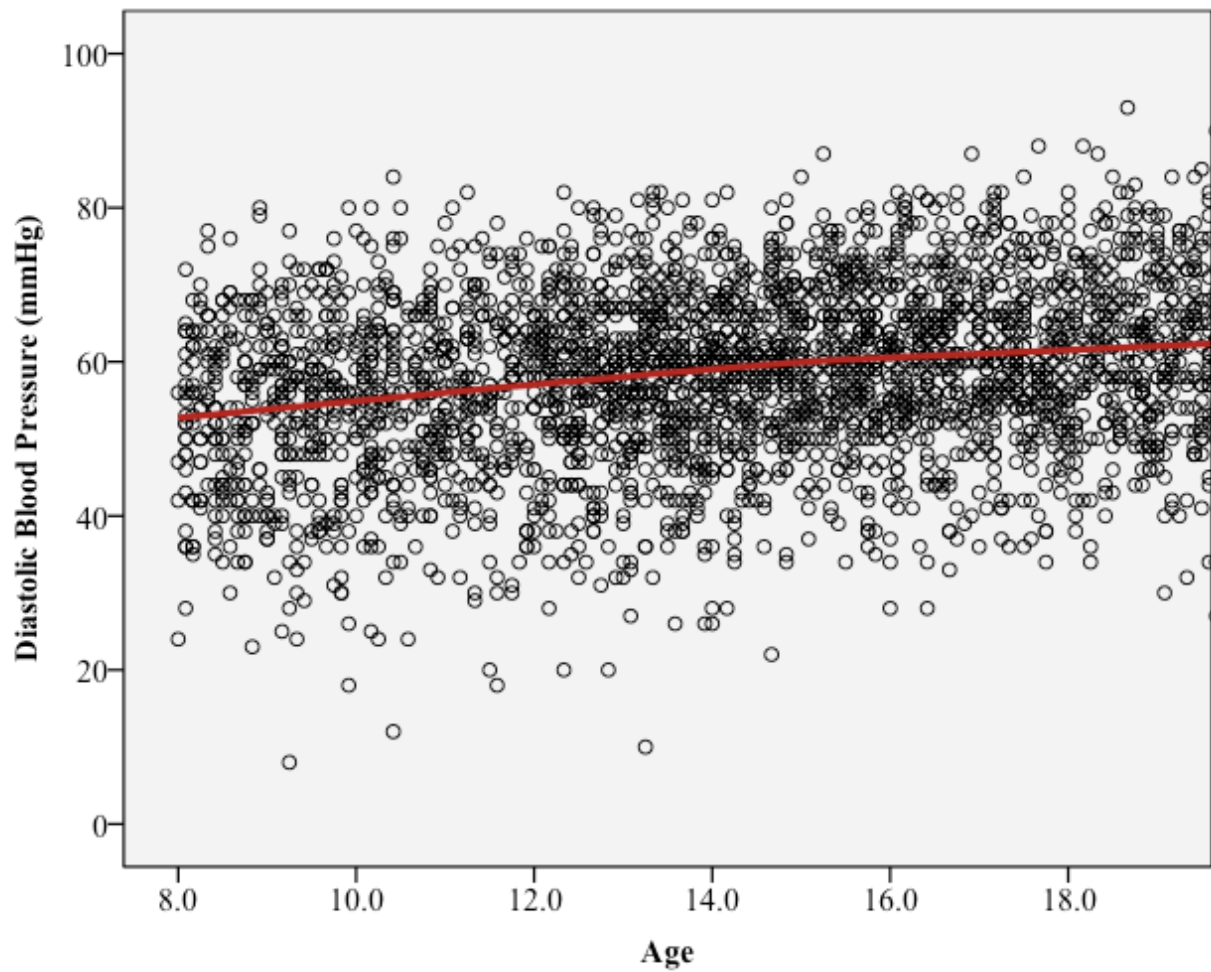


Figure 5. Distribution of mean arterial pressure by age in the total sample. Line of best fit (Loess method) is included.

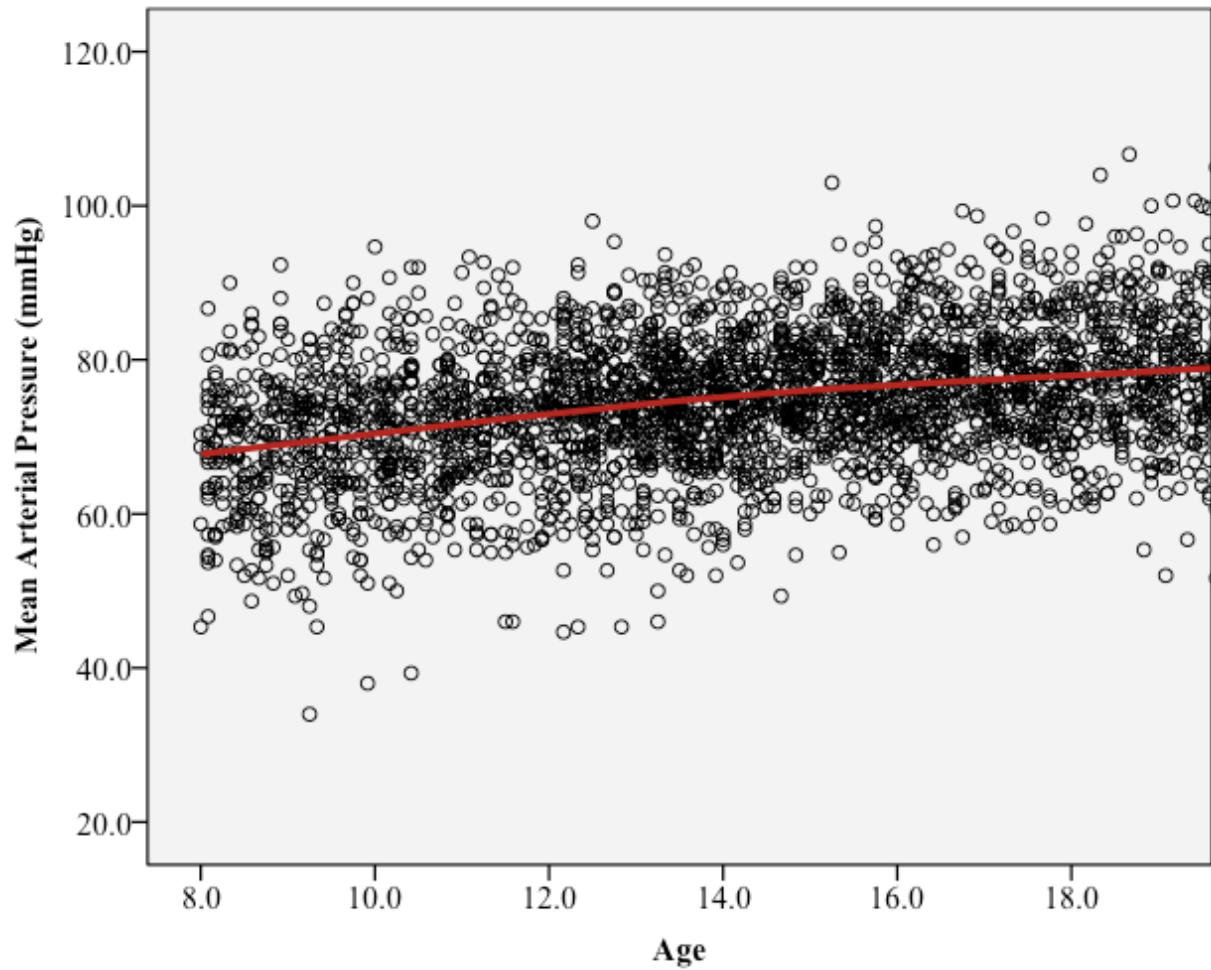


Figure 6. Systolic blood pressure by fatness-activity group. Least square mean and standard errors.

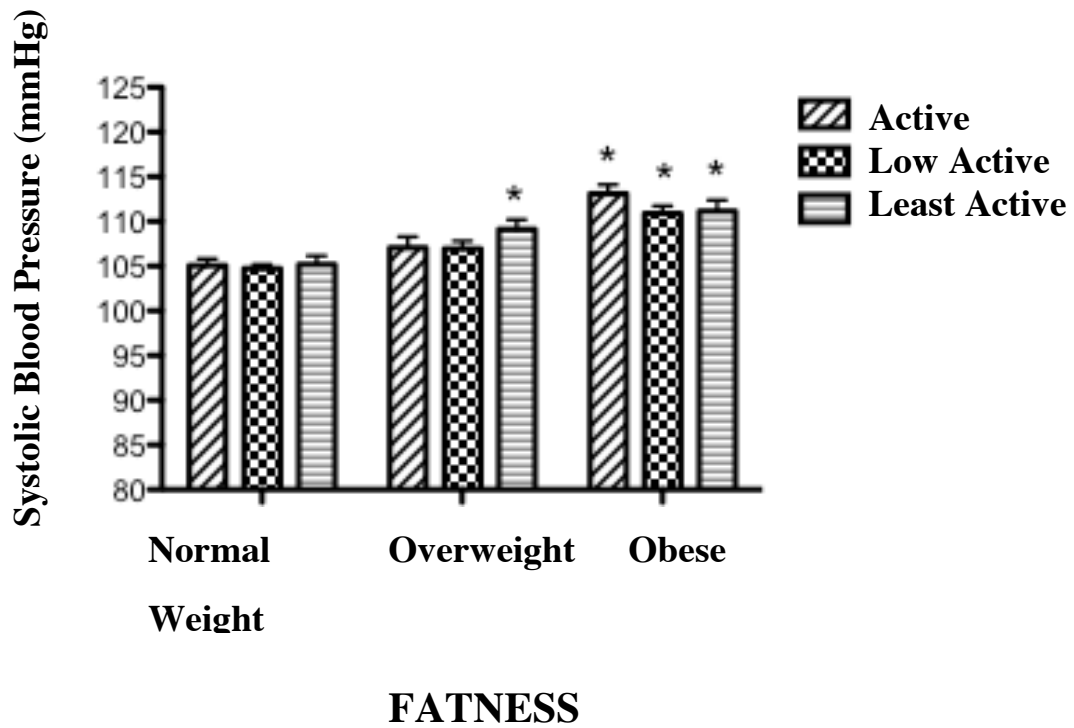


Figure 7. Diastolic blood pressure by fatness-activity group. Least square mean and standard errors.

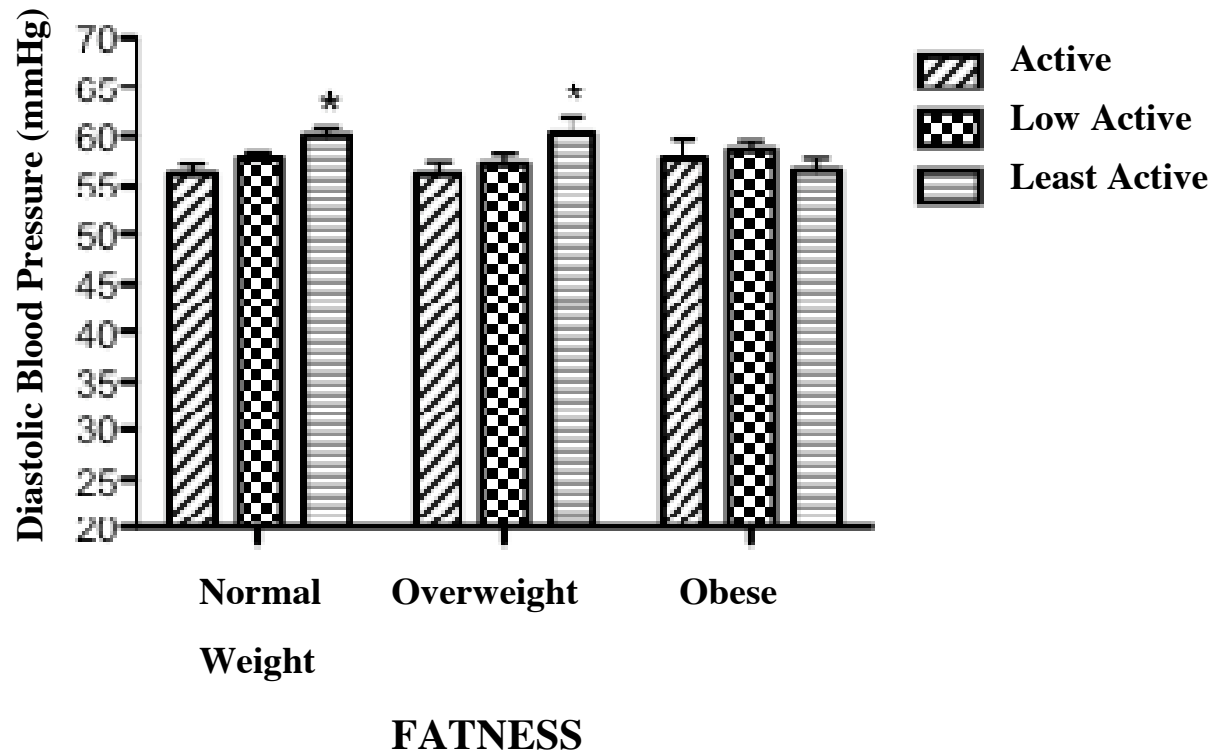
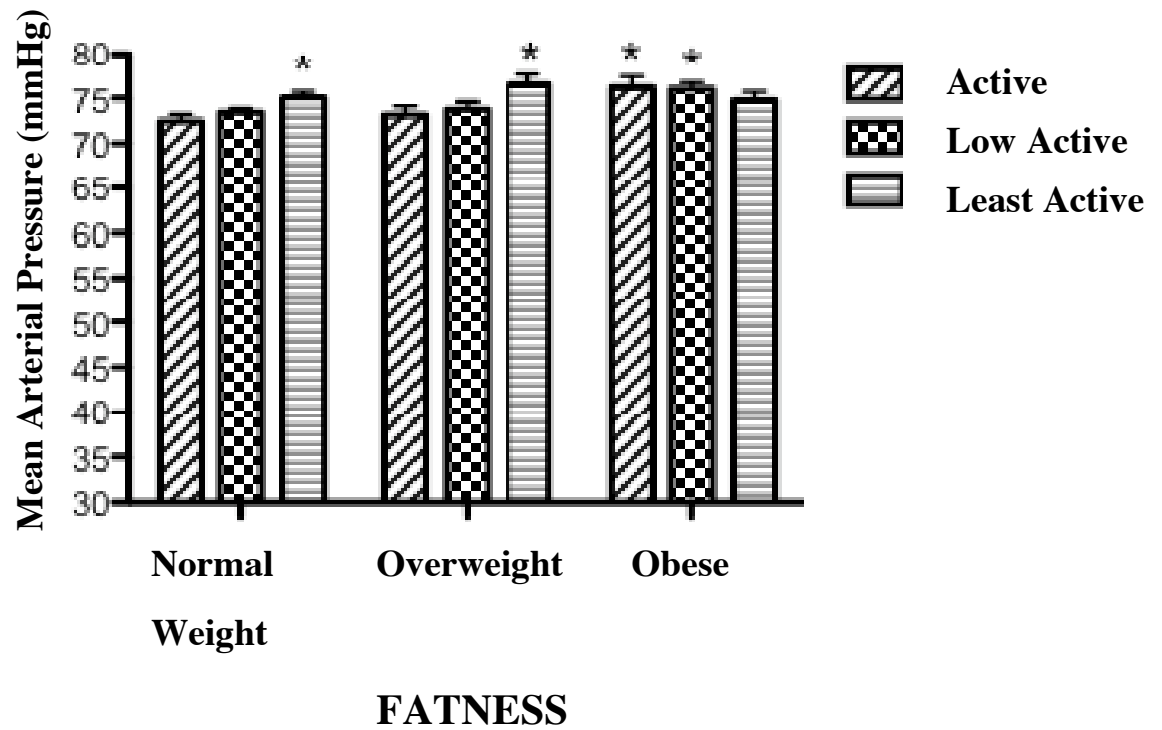


Figure 8. Mean arterial blood pressure by fatness-activity group. Least square mean and standard errors.



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CHAPTER 3

PHYSICAL ACTIVITY, ADIPOSITY, AND RESTING BLOOD PRESSURE IN 8-18 YEAR OLDS: THE EAST OF ENGLAND HEALTHY HEARTS STUDY.

INTRODUCTION

Atherosclerotic plaque is the primary cause of heart attacks and strokes (1), and the development of atherosclerotic fatty streaks and lesions has been clearly shown to begin early in life (1, 2). Excess adiposity or high body mass index (BMI) is a major risk factor for the development of atherosclerotic plaque (3) and elevated blood pressure (4-7). Obesity and elevated blood pressure during childhood are important concerns given that both track into adulthood (8), and in turn are both related to increased rates of cardiovascular disease (CVD) morbidity and mortality (9). Since CVD is the leading cause of death in many countries throughout the world, the prevention of atherosclerosis and other CVD risk factors remains a priority in both primary care settings and public health interventions, with an increased focus on overweight and obese children and adolescents.

A major strategy in the prevention of atherosclerosis is achieving the daily recommendation for physical activity (10). It is recommended that children and adolescents engage in 60 minutes per day of moderate-to-vigorous physical activity (MVPA), which should include vigorous-intensity physical activity at least three days a week (11). In the United Kingdom (UK) 5.1% and 0.4% of 11-year old boys and girls, respectively, accumulate 60 minutes of MVPA per day (12). The low prevalence of physical activity coupled with the high prevalence of overweight and obesity (32.3% of 11-15 year olds in the UK) (13) is a combination that has serious implications on CVD risk factors. In general, there is a moderate,

positive relationship between fatness and blood pressure (14, 15) and an inverse association between habitual physical activity and blood pressure in children and adolescents (16, 17). However, few studies (6, 18) have examined the combined association (interaction) of fatness and physical activity on CVD risk factors in youth.

Our previous work explored the combined association of physical activity with fatness on blood pressure in two separate groups of subjects. Results showed a strong association between fatness and blood pressure in 5 to 9 year olds (19) and 9 to 12 year olds (20), with no combined association between fatness and physical activity in either study. However, each study had limitations, including small sample size (n=91-174), a low percentage of obese subjects, and the use of self-reported physical activity. In a similar study, Parrett et al. (18) investigated the combined association between fatness and physical activity on another CVD risk factor, C-reactive protein, in pre-pubescent children (mean 9.4 years) and found a main effect for both fatness and physical activity, but no combined association. While there was no combined association, the authors concluded that habitual physical activity and fatness should be a focus in interventions designed to address chronic systemic inflammation and CVD risk factors in children.

Physiological functions, including blood pressure, are known to be influenced by gender and age. In both animal (21, 22) and human studies (23-25), it has been shown that blood pressure in males is consistently higher than pre-menopausal women of similar age. This age difference decreases in older adults, as women in their 60's and 70's have an increased likelihood of being diagnosed with hypertension post-menopause (26). This pattern of males having a higher blood pressure than females has also been seen in studies of children and adolescents (27). The relationship between age and blood pressure also has been examined and

the prevalence of hypertension has been shown to increase with age. It is estimated that greater than 50% of adults age 60 to 69 years and 75% of those over the age of 70 years have hypertension (28). Given that there is an association between fatness and blood pressure and that overweight and obesity track from childhood into adulthood (29-31), dependence on weight loss as a key in the treatment of CVD risk factors seems impractical; prevention is a preferred strategy. Interventions that focus on overweight or obese children and adolescents could benefit from a greater understanding of how meeting the recommended level of physical activity, without change in weight status, influences CVD risk factors. Therefore, the purpose of this study was to examine the independent and combined association (interactions) of physical activity and fatness with resting blood pressure in a large sample of 8-18 year old children and adolescents from the UK. It was hypothesized that there would be a positive relationship between fatness and resting blood pressure, an inverse relationship between physical activity and resting blood pressure, and an interaction between fatness and physical activity with blood pressure. Additionally, it was hypothesized that both sex and age differences would be apparent with older subjects (age 12 to 18) and boys (overall) having higher resting blood pressure than the younger subjects (age 8 to 11) and girls, respectively. This investigation extends previous research due to use of a significantly larger sample size.

METHODS

Subjects

Data from 7246 (3789 boys, 3457 girls) children and adolescents aged 8 to 18 years who participated in the East of England Healthy Hearts study during the summers of 2007 and 2008 were used for this secondary data analysis. The East of England Healthy Hearts Study is one of

the largest pediatric health studies in the UK (32). Participants were non-randomly recruited from 23 schools and were representative (mix of ethnicities and dwelling type – rural and urban) of the eastern area of England. Dwelling type was classified according to the UK National Statistics Postcode Directory classification. Urban was defined as densely populated areas with greater than 10,000 inhabitants. Rural included town and fringe (small towns and fringe areas that are located within the rural area), villages and isolated dwellings. Participants self-reported ethnicity. Diagnosed cardiovascular disease was the only exclusion criteria. Parental consent and child assent were obtained prior to data collection. The University of Essex ethics committee approved the data collection protocol. The analysis of the data from the East of England Healthy Hearts study was not submitted to the Michigan State University Institutional Review Board for approval, as it did not meet the criteria for involving human subjects (the data were de-identified for all analyses).

Measurements

Anthropometry. Each child's height was measured to the nearest 0.1cm (Seca Leicester Portable Stadiometer; Seca GmbH & Co. KG., Hamburg, Germany) and weight to the nearest 0.1kg (Seca 888 Compact Digital Floor Scale; Seca GmbH & Co. KG., Hamburg, Germany) without shoes and in shorts and t-shirt. BMI (kg/m^2) was calculated from measured height and weight, and BMI z-scores and percentiles were calculated from UK reference values (33). Participants were classified as underweight, normal weight, overweight, or obese based on International Obesity Task Force (IOTF) criteria (33).

Habitual Physical Activity. Every participant completed the Physical Activity Questionnaire for Adolescents (PAQ-A) (34) (participants ≥ 11 years) or Older Children (PAQ-

C) (35) (participants <11 years). Both questionnaires have the same questions and scoring system, except the PAQ-A does not ask about physical activity during morning recess. The PAQ-A and PAQ-C are 10 item questionnaires, with nine questions used to calculate a summary physical activity score, while the last question is used to determine whether illness or other events have prevented participants from participating in their normal level of activity over the previous week. Physical activity was defined in the questionnaire as sports, games, or dance that makes the participants breathe hard, makes their legs tired, or that makes them sweat. The nine items are scored on a five-point scale with higher scores equaling higher levels of activity. Six of the items assess physical activity in physical education classes, at recess, during lunch, after school, in the evenings, and on the weekends. Both the PAQ-A and PAQ-C have been shown to possess good reliability ($r=0.72-0.88$) and moderate validity ($r=0.56$ and 0.63) in this age group (36). Based on their physical activity questionnaire (PAQ) score, participants were classified as low active (PAQ score of 1-2), moderately active (PAQ score of 3), or active (PAQ score of 4-5) (37).

Blood Pressure. Blood pressure was measured following 10-12 minutes of seated rest in which the participants were asked to sit quietly with feet on the ground and their arm resting on a table. Cuff size was determined for each individual participant and placed around the upper left arm. Blood pressure was measured twice by an automated sphygmomanometer (Omron MX3, Japan). The Omron MX3 has been shown to be reliable in youth according to the British Hypertension Society criteria (38). The lower of the two measures was recorded to account for any elevation in blood pressure due to anxiety. From measured systolic blood pressure (SBP) and diastolic blood pressure (DBP), mean arterial pressure (MAP) was calculated as $MAP = .66 (DBP) + .33 (SBP)$. Standardized scores (MAP z-scores) adjusting for age, sex, and skewness

were derived using UK blood pressure reference charts (39). MAP z-scores were used as the outcome variable in the linear regression models as they take into consideration age and sex. MAP percentiles were calculated and subjects were classified as having high-normal blood pressure ($\geq 91^{\text{st}}$ MAP percentile < 98^{th} MAP percentile) or as hypertensive ($\geq 98^{\text{th}}$ MAP percentile) (39).

DATA ANALYSIS

Descriptive characteristics were calculated for the total sample and by sex and age groups (8-11 years and 12-18 years). Differences by age groups and sex were examined by analysis of covariance (ANCOVA), controlling for sex and age, respectively. Differences in categorical variables (physical activity, blood pressure, and fatness) were examined by Chi-Square. Pearson correlations between continuous values for fatness, physical activity, and MAP z-scores were computed. The combined association of fatness and physical activity with MAP z-scores was analyzed by a 3 x 4 ANCOVA (physical activity x fatness) in the total sample, in boys and girls, and in 8 to 11 and 12 to 18 year olds, controlling for dwelling and ethnicity. Logistic regression was performed to determine the association of sex, age, fatness, and physical activity with the odds of having high-normal blood pressure and with the odds of having hypertension. Statistical analyses were performed using SPSS version 19 (IBM, Somers, NY) with the level of significance set at $p < 0.05$.

RESULTS

The sample was predominantly white (89.7%) and from urban areas (54.9%). Descriptive characteristics of the sample are shown in Table 8a and 8b and the distribution of PAQ scores and BMI by age are shown in Figures 9 and 10. Overall, boys were significantly older and taller

than girls ($p<0.05$) but girls' BMI was higher. Based on IOTF cut points, 4.2% of the subjects were underweight, 67.3% normal weight, 22.1% overweight, and 6.3% obese. Percentage of participants by fatness classification (underweight, normal weight, overweight, and obese) did not differ between boys and girls ($p=0.263$), but 8 to 11 year olds had a significantly lower percentage of normal weight participants (63.4% vs. 68.7%) and a higher percentage of both overweight (24.6% vs. 21.2%) and obese (7.9% vs. 5.8%) participants ($p<0.001$) than the 12 to 18 year olds.

The mean SBP approximated the 59th percentile, DBP the 80th percentile, and MAP the 66th percentile with 13.4% classified as having high-normal blood pressure ($\text{MAP} \geq 91^{\text{st}}$ percentile < 98th percentile) and 7.5% as having hypertension ($\text{MAP} \geq 98^{\text{th}}$ percentile). The distribution of MAP scores by BMI and PAQ score are shown in Figures 11 and 12. There was a significant sex difference in both SBP and DBP between 12 to 18 year old boys and girls (Table 8b). Boys had significantly higher SBP, but lower DBP than girls. SBP (higher) and DBP (lower) were significantly different between younger and older boys, but not younger and older girls. MAP was significantly different between boys and girls in both age categories and between younger and older boys. There was a significant ($p<0.01$) positive correlation between BMI and MAP z-score ($r=0.238$), controlling for PAQ score, and negative correlation between PAQ score and MAP z-score (-0.059), controlling for BMI.

Fifty-nine percent of all participants were classified as low active with girls (70%) significantly more likely to be low active than boys (49%) ($p<0.001$). Only 5.8% of participants were classified as active, with a greater percentage of boys (8.4%) being classified as active compared to girls (2.8%) ($p<0.001$). Of the participants classified as active, 2.2% were obese and

16.1% as overweight, while 65.3% of participants classified as low active were normal weight. The prevalence of high-normal blood pressure and hypertension in active participants was 9.1% and 8.2%, respectively, while those classified as low active had a prevalence of 14.5% and 5.8%, respectively.

Main effects for physical activity and fatness and the combined association (interaction) of physical activity and fatness on MAP z-scores were analyzed. There was a main effect for fatness in each analysis – total sample ($F(3, 6270)=29.727, p<0.05$), boys ($F(3, 3230)=22.946, p<0.05$), girls ($F(3, 3026)=7.243, p<0.05$), 8 to 11 year olds ($F(3, 1625)=8.152, p<0.05$), and 12-18 year olds ($F(3, 4631)=22.670, p<0.05$). Results for total sample showed that obese subjects had significantly higher MAP ($89.6\pm0.4\text{mmHg}$) than those in the overweight ($86.9\pm0.2\text{mmHg}$) and normal weight ($83.6\pm0.1\text{mmHg}$) groups, and subjects in the overweight group also had a significantly higher MAP than those in the normal weight group. MAP values by weight status-activity groups are shown in Figures 13 through 17. A main effect for physical activity was only significant in the total sample ($F(2, 6270)=4.553, p<0.05$), in girls ($F(2, 3026)=3.549, p<0.05$), and in subjects aged 12 to 18 years ($F(2, 4631)=4.703, p<0.05$). Subjects in the low active group had a significantly higher MAP ($85.1\pm0.1\text{mmHg}$) than those in both the moderately active ($84.1\pm0.2\text{mmHg}$) and active group ($83.0\pm0.5\text{mmHg}$). No combined association of physical activity and fatness was found in any of the analyses.

Results of the logistic regression are shown for odds of having high normal blood pressure (Table 9a) and hypertension (Table 9b). Obesity was the strongest predictor of high normal blood pressure (odds ratio (OR) = 3.23, CI = 2.54-4.11) and hypertension (OR = 4.79, CI = 3.64-6.31). In both boys and girls, fatness was an important determinant of both high-normal blood pressure and hypertension. Compared to normal weight boys and girls, those who were

obese had an odds ratio of 3.73 (CI = 2.71-5.14) and 2.67 (CI = 1.85-3.84), respectively, and overweight boys and girls were almost two times more likely to possess high-normal blood pressure. In relation to hypertension, overweight increased the risk in both boys and girls by over two times, and being obese led to an odds ratio of 5.97 (CI = 4.13-8.62) in boys and 3.61 (CI = 2.37-5.52) in girls. Being underweight offered a level of protection in boys from having high-normal blood pressure (OR = 0.45, CI = 0.23-0.89) and in girls from becoming hypertensive (OR = 0.20, CI = 0.05-0.80).

DISCUSSION

This study examined the independent and combined associations between physical activity and fatness with blood pressure in a large sample of children and adolescents. To our knowledge, the combined association (interaction) between fatness and physical activity on blood pressure has not been examined in such a large sample of children and adolescents, making the results of this study novel and a strong contribution to the literature. The results of this study supported our hypothesis that there would be a positive relationship between fatness and resting blood pressure and an inverse relationship between physical activity and resting blood pressure. Additionally, the results supported the hypothesis that older youth (ages 12 to 18 years) would have higher resting blood pressure than younger youth (ages 8 to 11 years). No combined association between fatness and physical activity on blood pressure was found, and girls had higher resting blood pressure than boys, neither finding supporting the hypotheses put forth prior to data analysis.

The relationship between fatness and blood pressure has been well documented in both children and adolescents and the results of this study are consistent with that literature (7, 14, 40,

41). The main effect for fatness was significant in each analysis and in boys and girls; overweight and obesity significantly increased the odds of having high-normal blood pressure (overweight: OR = 1.74 (CI = 1.40-2.17) & 2.04 (CI = 1.63-2.57), respectively; obesity: OR = 3.73 (CI = 2.71-5.14) & 2.67 (CI = 1.85-3.84), respectively), and hypertension (overweight: OR = 2.16 (CI = 1.62-2.87) & 2.32 (CI = 1.74-3.09), respectively; obesity: OR = 5.97 (CI = 4.13-8.62) & 3.61 (CI = 2.37-5.52), respectively), in accordance with previous research (42). These results were shown despite the sample having a lower prevalence of overweight and obesity than UK national averages (28.4% vs. 32%). Results from NHANES 1988-2006 (43) indicated that weight status was positively associated with blood pressure in 8-12 year old children, with overweight boys (OR = 1.54, CI = 1.11-2.13) and obese boys and girls (OR = 2.81, CI = 2.13-3.71 and OR = 2.55, CI = 1.75-3.73, respectively) being significantly more likely to be pre-hypertensive than normal weight youth. The likelihood of being hypertensive was also significantly greater in both overweight and obese boys (OR = 6.06, CI = 2.73-13.44) and obese girls (OR = 2.33, CI = 1.31-4.13). Both elevated blood pressure and high BMI have been shown to contribute to an increase in left ventricular mass (44), which may ultimately lead to a diagnosis of left ventricular hypertrophy (45, 46). The relationship between fatness and blood pressure, shown in this study and the literature, needs to be addressed in interventions that focus on reducing CVD risk factors in children and adolescents.

It is important to note that the difference in MAP (6 mmHg) between the normal weight group and the obese group was both statistically and clinically significant. Results from a large intervention study have shown that a 5 mmHg reduction in blood pressure can decrease mortality due to coronary heart disease, cardiovascular disease, and all cause mortality by 10.5%, 11.3%, and 7.9% respectively (47). Ideally, it would be most beneficial to focus on all children and

adolescents who are overweight and obese to try to reduce their fatness to normal levels. From a practical standpoint, being able to take a child from being obese to overweight might make meeting the overall goal of reaching normal weight status more manageable. Setting a goal too high and an unreasonable timetable can lead to sense of failure and may lead to more struggle the next time that person works toward achieving a healthy weight and fatness level.

Encouraging physical activity in children and adolescents of all levels of fatness is important as it has been shown that physical activity is beneficial to reducing numerous cardiovascular risk factors, not just blood pressure (48-50). While there was a significant inverse relationship between physical activity and MAP, the clinical significance of the difference (2 mmHg) between the low physical activity group and the active group was not strong. In the current study, boys were more active than girls, and participants in the younger age category had higher PAQ scores than older participants. Crocker et al. (51) reported similar findings using the PAQ-C in older children (ages 8 to 14 years). A dramatic age-related decline in minutes of MVPA from childhood to adolescence has been documented in the United States (52), and the PAQ scores from this cohort follow that pattern with the proportion of 8 to 11 year olds categorized with low activity at 53.3% and 61.4% in 12 to 18 year olds. The results showed that if boys and girls increased their PAQ score by one point, it would lead to an 18% decrease in the odds of having hypertension. This protective effect of physical activity was only seen in boys (OR = 0.82, CI = 0.68-0.98) in relation to having hypertension. The inclusion of physical activity in a child's day must be made a priority, especially those who are overweight and obese. Exercise training studies (53-55) have shown improvements in vascular function, measured by flow mediated dilation, without a decrease in body weight or body fat indicating that beneficial physiological changes occur from physical activity without weight loss or improved body

composition. Our findings are important and suggest that intervention programs need to focus both on reducing fatness and improving physical activity, as both impact blood pressure and overall vascular health. Although encouraging physical activity at all ages is important, the transitional period between childhood and adolescence may be a critical time point given the age-related trend in physical activity. Physical activity promotion in children and adolescents should be through a variety of avenues including, but not limited to, physical education in school, opportunities to participate on community-based teams, or access to green space and safe playgrounds.

Age and sex differences were also explored in this sample. Overall, being in the older age category increased the risk of having high normal blood pressure in boys (OR = 1.68, CI = 1.32-2.14) and girls (OR = 1.29, CI = 1.02-1.64) and hypertension in boys only (OR = 1.48, CI = 1.09-2.01). Contrary to the previous research (27, 56), MAP was significantly lower in boys in the 12 to 18 year old category when compared with boys in the 8 to 11 year old category, and girls had significantly higher MAP in both the younger group and the older group compared to similar aged boys. As there was no measure of maturation in this sample, these results may be skewed, as they are contrary to the current literature. Future research should include a measure of maturation to better examine the relationship between age and sex and blood pressure.

In this study, there was no combined association between fatness and physical activity on our outcome measures. Many factors that could influence this complex relationship were not examined in this study, including family history, prenatal and birth data, and dietary history. Indeed, the heritability of blood pressure has been shown to be between 30-50% (57). Diet, the other major behavioral risk factor for CVD, can have both a positive and negative influence on fatness and blood pressure. Increase in total fat consumption has shown to be related to poorer

quality of diet (58-60) and also associated with measures of fat mass (BMI, skinfold) (61-63). Ortega et al. (64) reported that the overweight/obese subjects consumed more of their energy from protein and fats and less from carbohydrates compared to the normal weight controls, while Hassapidou et al. (60) reported that the overweight/obese subjects in a cohort of Greek adolescents consumed less fat, protein, and carbohydrates compared to normal weight adolescents. High intake of dietary fiber has also been shown to be inversely associated with metabolic syndrome in a large sample of adolescents (65). Omega-3 fatty acids have been recognized as an anti-inflammatory nutrient, with both observational studies (66-69) and interventional studies (70-72) showing inverse relationships between the consumption of these fatty acids and the reduction of inflammatory markers, including CRP. These factors often work in conjunction, and possibly synergistically, thereby increasing the need for studies that focus on the combined association of multiple determinants.

By clearly understanding the influence that fatness and physical activity have on blood pressure, both independently and jointly, interventionists and primary care health/medical providers can tailor programs to extract the most benefit from decreasing fatness and improving physical activity levels, while also addressing additional factors that could be influencing blood pressure values. Multi-level interventions that address a larger proportion of a child or adolescent's environment (school, home, and community), while also examining factors such as maternal influences and dietary trends may see a greater impact on changing CVD risk factors in children most at risk, namely those who are overweight or obese and those who are not meeting physical activity recommendations.

A major strength of this study was the large sample size (>7000 children and adolescents), which allowed for sex- and age-specific analyses. A limitation was the self-

reported physical activity. An objective measure of physical activity (e.g., accelerometry) would have allowed for examination of physical activity intensity and determination of a threshold or cut point for the amount of physical activity necessary to attenuate the influence of fatness on MAP. Classifying fatness by BMI may also have led to misclassification bias, as BMI is a measure of the relationship between body weight and body height, and does not differentiate between muscle mass, fat mass, or skeletal mass, and has been shown to produce errors when estimating body fatness (73). Using a reference method (i.e., hydrostatic weighing, dual-emission X-ray absorptiometry, etc.) would have been ideal, but with the large sample size and the cost associated with such methods, it was not feasible. No measure of maturation was performed, which also could have lead to misclassification bias as we separated by age category. Additionally, data were cross-sectional so no causation can be inferred.

CONCLUSION

While there was no combined association (interaction) between physical activity and fatness, fatness clearly had the strongest influence on blood pressure. Given the current prevalence rates of overweight and obesity and physical inactivity in children and adolescents, programs that focus on decreasing overall fatness, preventing excess weight gain, and increasing daily physical activity should be emphasized. These programs must address the influence of the school, family, and community, and need to consider how all of these environments can help improve the overall vascular health, and physical activity habits of children and adolescents. Future research is warranted to better understand how total dose of physical activity and differing intensities of physical activity potentially have a protective effect on CVD risk factors. In particular, longitudinal research could better explore the change in blood pressure related to various intensities of physical activity. While the current national guidelines for physical activity

state that children and adolescents should be accumulating 60 minutes per day of MVPA, it may be that for those who are overweight or obese and who have high-normal blood pressure, or even hypertension, a larger dose of physical activity is needed to see changes in blood pressure. Many questions still need to be answered and many children and adolescents will benefit from clear and concise answers.

APPENDIX

APPENDIX

Table 8a. Descriptive characteristics of the total sample. Values are mean (SD) and range.

	Boys (n=3789)	Girls (n=3457)	Total (n=7246)
Age	13.1 (1.5)* 8.8-18.7	13.0 (1.4) 8.8-18.3	13.1 (1.4) 8.8-18.7
Height (cm)	157.7 (12.2)* 122.0-195.0	155.2 (8.6) 124.0-190.7	156.5 (10.7) 122.0-195.0
Weight (kg)	51.4 (14.0) 21.2-121.1	50.1 (11.6) 23.5-166.2	50.8 (12.9) 21.2-166.2
BMI (kg/m²)	20.4 (3.7)* 11.5-41.3	20.6 (3.7) 11.3-45.7	20.5 (3.7) 11.3-45.7
Systolic Blood Pressure (mmHg)	118.1 (14.1)* 51.0-199.0	116.5 (12.8) 55.0-189.0	117.3 (13.5) 51.0-199.0
Diastolic Blood Pressure (mm Hg)	67.2 (10.7)* 22.0-160.0	69.5 (10.7) 21.0-117.0	68.3 (10.8) 21.0-160.0
Mean Arterial Pressure (mmHg)	84.2 (10.0)* 44.3-162.3	85.2 (9.9) 42.3-134.7	84.7 (10.0) 42.3-162.3
High-Normal Blood Pressure	13.6%	13.2%	13.4%
Hypertension	7.5%	7.4%	7.5%
PAQ Score	3.0 (0.7)* 1.0-4.8	2.7 (0.6) 1.0-4.7	2.9 (0.7) 1.0-4.8

*Boys and girls significantly different (p<0.05)

Table 8b. Descriptive characteristics of the sample by sex and age. Values are mean (SD) and range.

	8-11 year olds			12-18 year olds			P-value for age groups	
	Boys n=948	Girls n=912	P = for sex	Boys N=2841	Girls n=2545	P = for sex	Girls	Boys
Age	11.3 (0.6)	11.4 (0.6)	0.646	13.7 (1.2)	13.6 (1.1)	0.028	0.039	0.038
Height (cm)	146.9 (7.8)	148.7 (8.0)	<0.001	161.3 (11.3)	157.6 (7.5)	<0.001	<0.001	<0.001
Weight (kg)	42.0 (10.3)	43.6 (10.6)	0.003	54.6 (13.6)	52.4 (11.0)	<0.001	<0.001	<0.001
BMI (kg/m ²)	19.3 (3.5)	19.6 (3.7)	0.060	20.7 (3.7)	21.0 (3.7)	0.005	<0.001	<0.001
Systolic Blood Pressure (mmHg)	117.4 (0.44)	117.5 (0.44)	0.910	117.6 (0.25)	116.9 (0.25)	0.040	0.242	<0.001
Diastolic Blood Pressure (mmHg)	68.0 (0.37)	69.6 (0.37)	0.001	66.7 (0.21)	69.8 (0.21)	<0.001	0.620	0.002
Mean Arterial Pressure (mmHg)	84.5 (0.33)	85.6 (0.33)	0.017	83.7 (0.19)	85.5 (0.19)	<0.001	0.879	0.031
High- Normal Blood Pressure	9.9%	11.5%		14.9%	13.8%			
Hyper- tension	6.2%	7.3%		7.9%	7.5%			
PAQ Score	3.1 (0.7)	2.8 (0.6)	<0.001	3.0 (0.7)	2.7 (0.6)	<0.001	<0.001	<0.001

Table 9a. Independent influences on the odds of having high normal blood pressure using Logistic Regression.

Odds Ratio (95% Confidence Interval)

Predictors	Total Sample (n=7246)	Boys (n=3789)	Girls (n=3457)
Sex			
<i>Boys</i>	1.0		
<i>Girls</i>	0.93 (0.81-1.07)		
Age			
<i>8-11 years</i>	1.0	1.0	1.0
<i>12-18 years</i>	1.48 (1.25-1.75)	1.68 (1.32-2.14)	1.29 (1.02-1.64)
Fatness			
<i>Normal Weight</i>	1.0	1.0	1.0
<i>Underweight</i>	0.59 (0.38-0.91)	0.45 (0.23-0.89)	0.73 (0.42-1.29)
<i>Overweight</i>	1.88 (1.61-2.20)	1.74 (1.40-2.17)	2.04 (1.63-2.57)
<i>Obese</i>	3.23 (2.54-4.11)	3.73 (2.71-5.14)	2.67 (1.85-3.84)
Physical Activity*	0.84 (0.75-0.93)	0.83 (0.72-0.95)	0.84 (0.71-0.99)

*Continuous PAQ Score

Table 9b. Independent influences on the odds of having hypertension using Logistic Regression.

Odds Ratio (95% Confidence Interval)

Predictors	Total Sample (n=7246)	Boys (n=3789)	Girls (n=3457)
Sex			
<i>Boys</i>	1.0		
<i>Girls</i>	0.95 (0.79-1.14)		
Age			
<i>8-11 years</i>	1.0	1.0	1.0
<i>12-18 years</i>	1.30 (1.05-1.61)	1.48 (1.09-2.01)	1.13 (0.84-1.52)
Fatness			
<i>Normal Weight</i>	1.0	1.0	1.0
<i>Underweight</i>	0.31 (0.14-0.69)	0.42 (0.15-1.15)	0.20 (0.05-0.80)
<i>Overweight</i>	2.24 (1.83-2.74)	2.16 (1.62-2.87)	2.32 (1.74-3.09)
<i>Obese</i>	4.79 (3.64-6.31)	5.97 (4.13-8.62)	3.61 (2.37-5.52)
Physical Activity*	0.82 (0.72-0.94)	0.82 (0.68-0.98)	0.82 (0.67-1.02)

*Continuous PAQ Score

Figure 9. Relationship of physical activity scores by age in the total sample (n=7246).

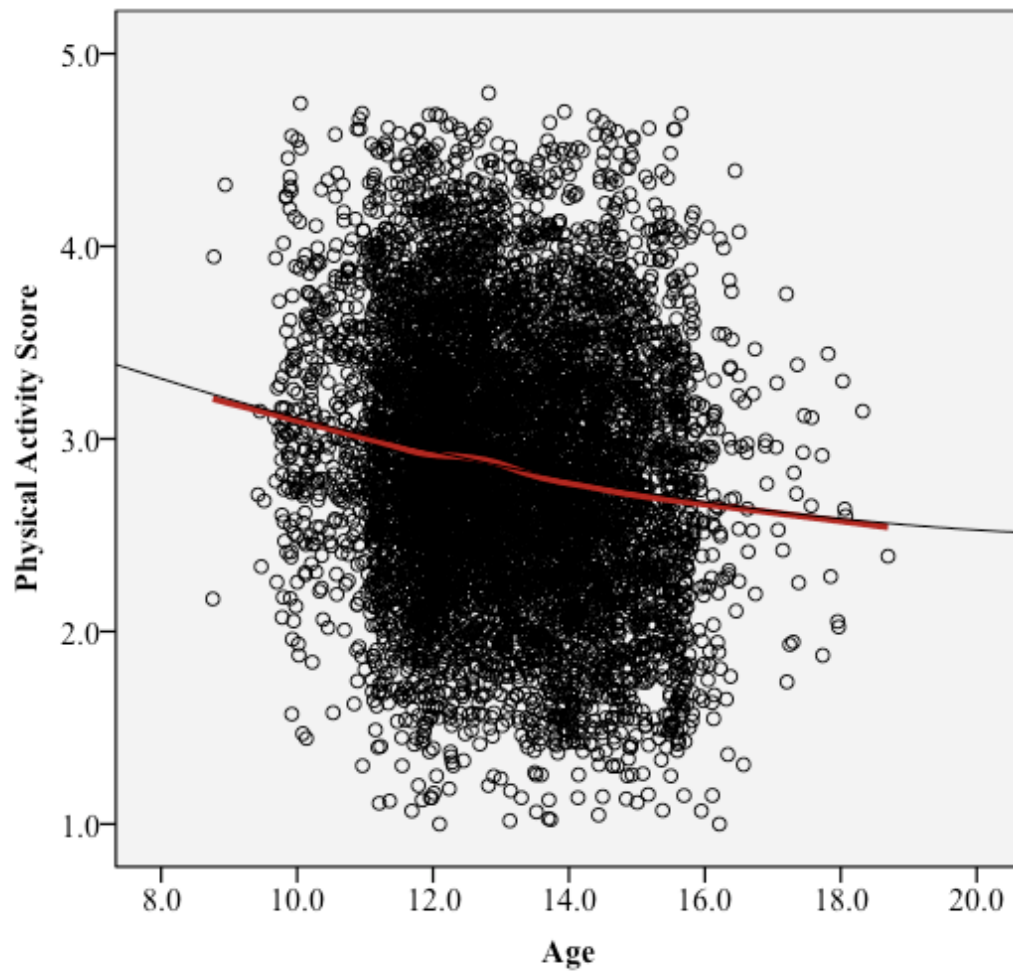


Figure 10. Relationship of BMI values by age in the total sample (n=7246).

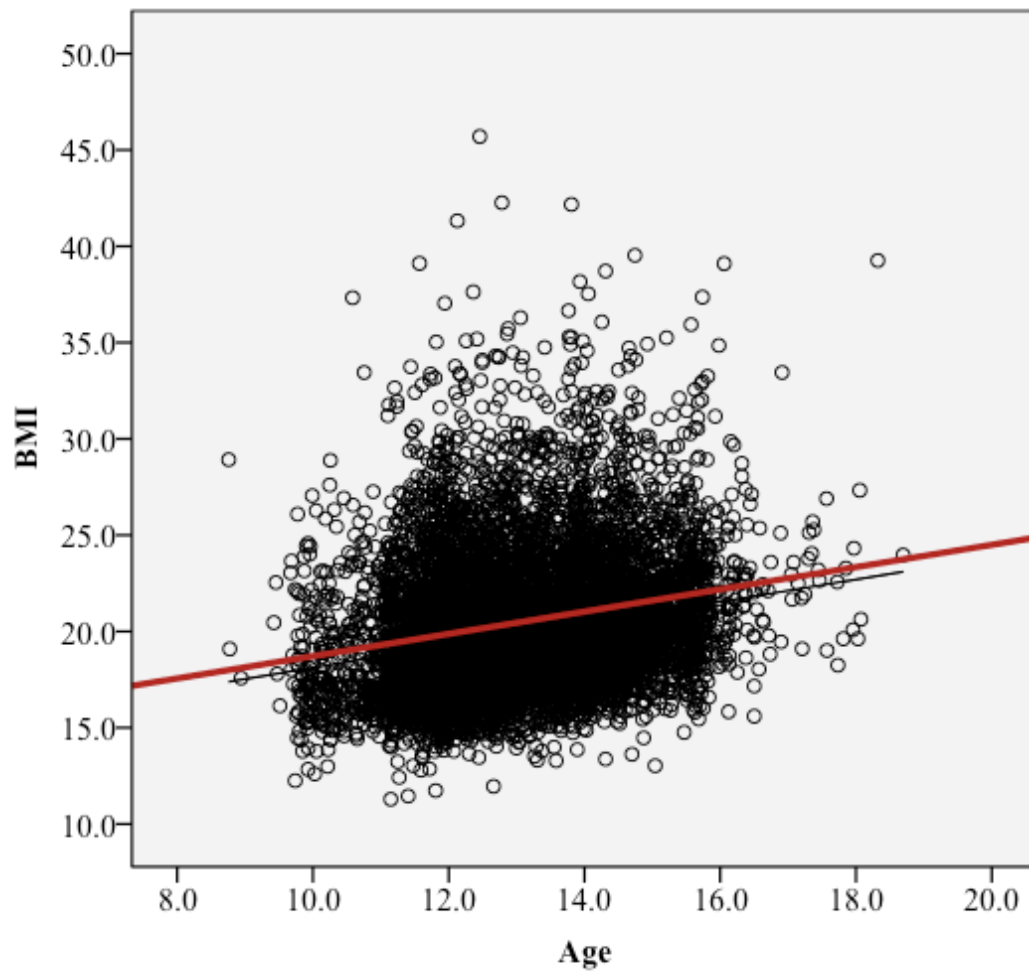


Figure 11. Relationship between mean arterial pressure and BMI – total sample (n=7246).

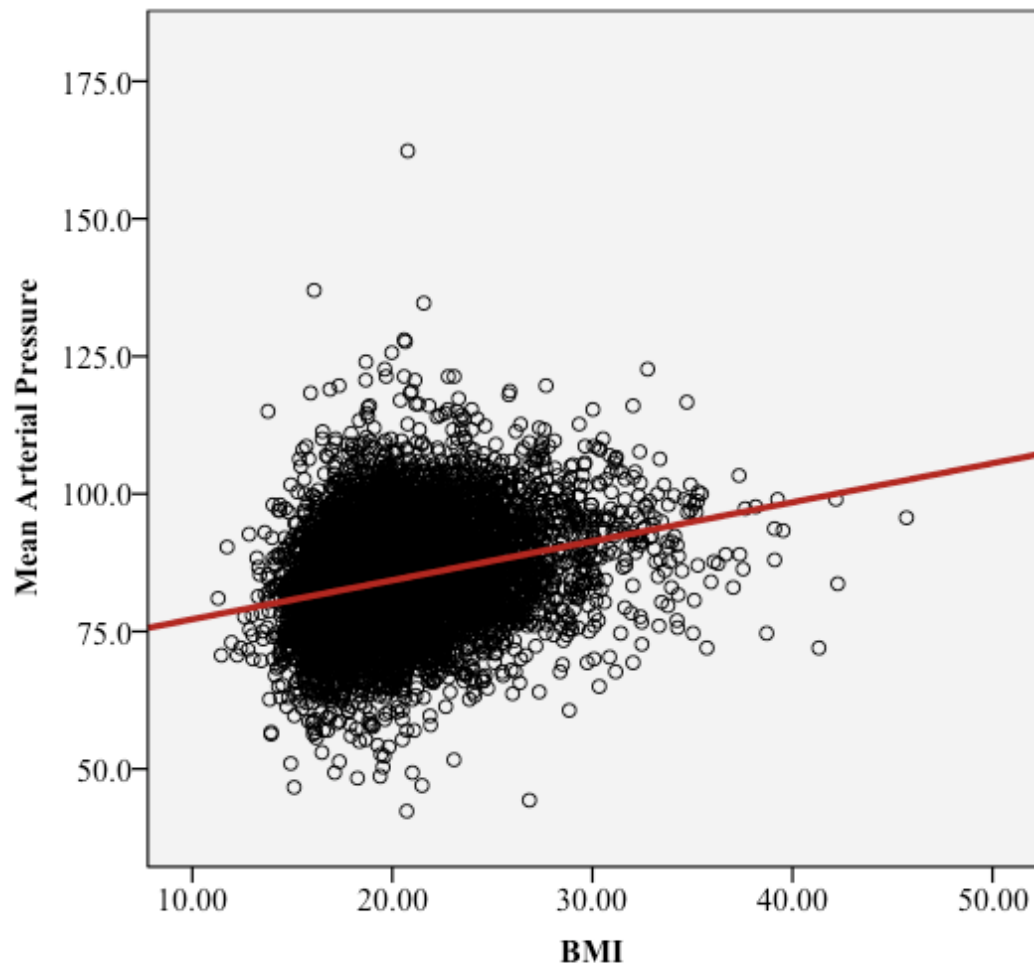


Figure 12. Relationship between mean arterial pressure and physical activity score – total sample (n=7246).

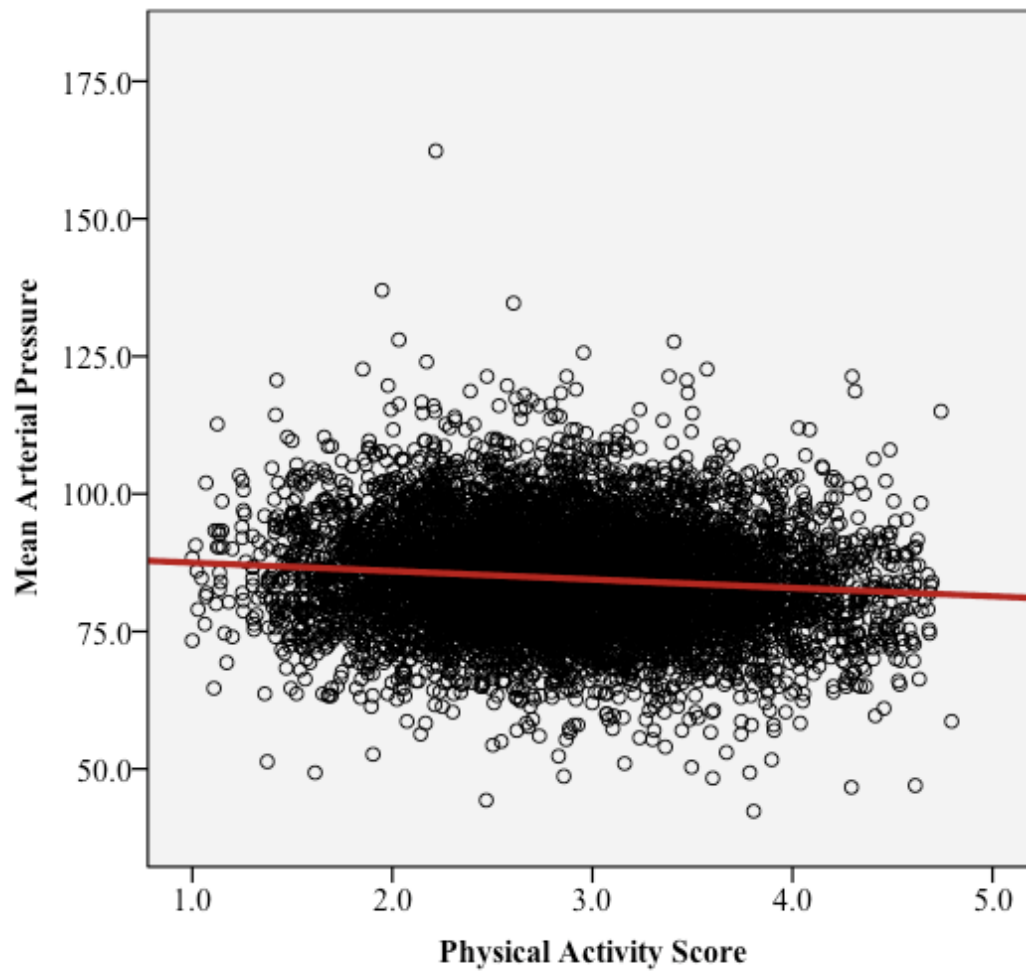


Figure 13. Mean arterial pressure by weight status-activity groups – all subjects.

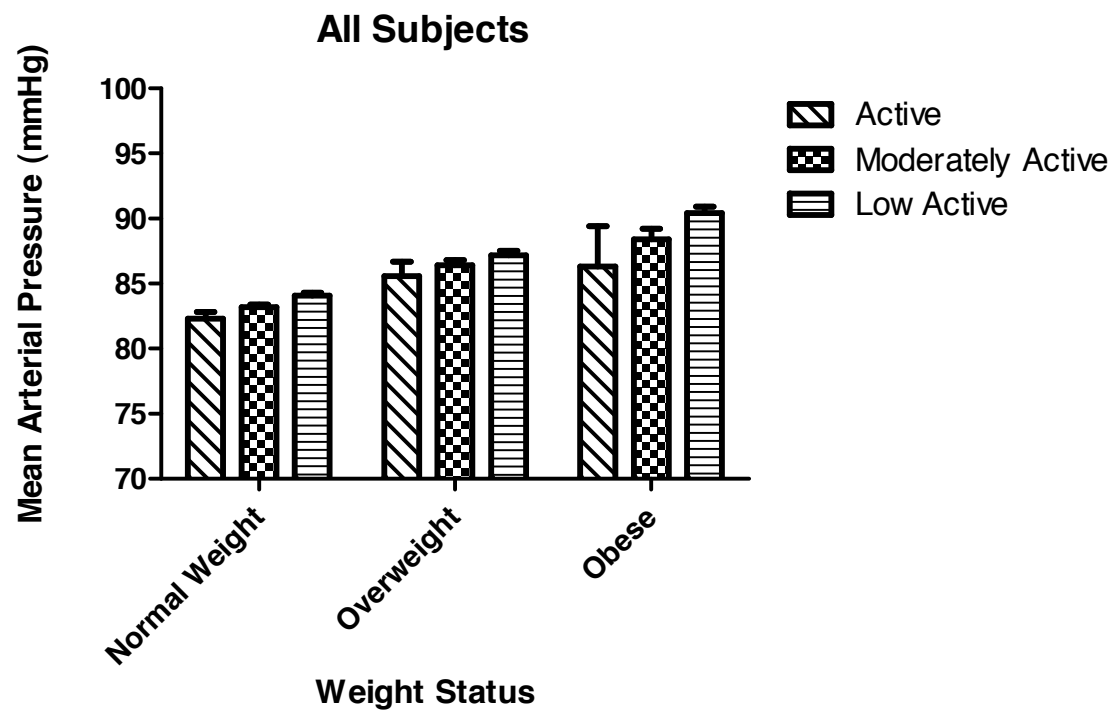


Figure 14. Mean arterial pressure by weight status-activity groups – boys.



Figure 15. Mean arterial pressure by weight status-activity groups – girls.

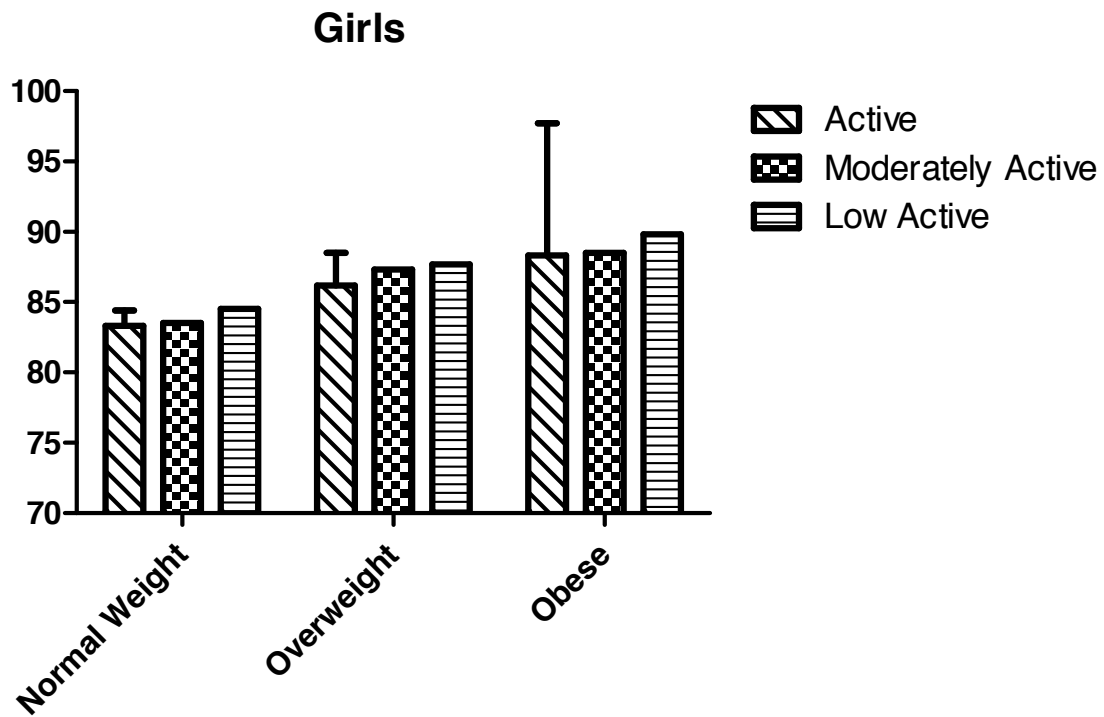


Figure 16. Mean arterial pressure by weight status-activity groups – 8 to 11 year olds.

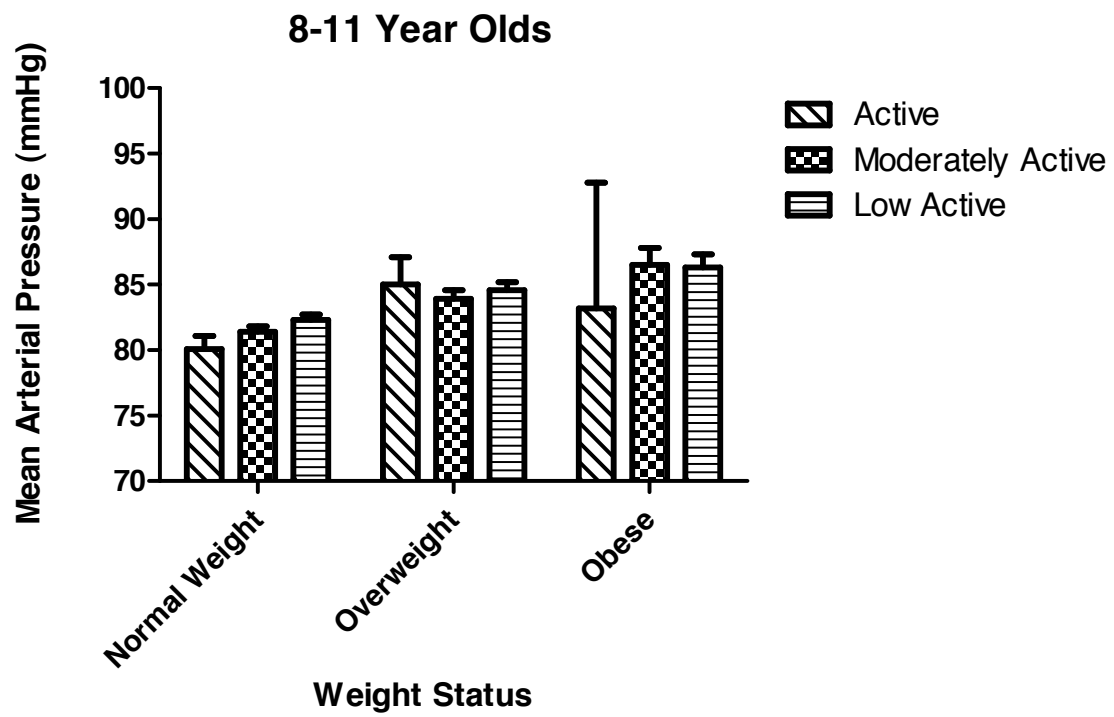


Figure 17. Mean arterial pressure by weight status-activity groups – 12 to 18 year olds.



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CHAPTER 4

FINAL CONCLUSIONS

The purpose of this dissertation was to examine the independent and combined association (interaction) of fatness and physical activity with blood pressure and C-reactive protein (CRP) in two nationally representative cohorts, the East of England Healthy Hearts Study (blood pressure only) from the United Kingdom (UK) and the National Health and Nutrition Examination Survey (NHANES) (blood pressure and CRP) from the United States (US). Additionally, the effect of age and gender on blood pressure and CRP was also examined. This dissertation allowed us to build on previous work, and the large size of both samples allowed us to address a limitation of those previous studies in order to better evaluate these relationships.

With regard to the main effect of fatness on blood pressure, it was hypothesized that a positive relationship would be observed. Indeed, a consistent, positive relationship between fatness and blood pressure was seen in each analysis in the East of England Healthy Hearts Study. With this sample, both age and gender were evaluated, and the positive relationship between fatness and blood pressure was seen in the total sample ($F(3, 6270)=29.727, p<0.05$), boys ($F(3, 3230)=22.946, p<0.05$), girls ($F(3, 3026)=7.243, p<0.05$), 8-11 year olds ($F(3, 1625)=8.152, p<0.05$), and 12-18 year olds ($F(3, 4631)=22.670, p<0.05$). A similar outcome was observed in the NHANES sample. Main effects for fatness were seen for systolic blood pressure (SBP) in the total sample (obese vs. normal weight: $\beta=8.03; p=0.0000$), boys (obese vs. normal weight: $\beta=9.37; p=0.0000$), and girls (obese vs. normal: $\beta=5.24; p=0.0332$), and mean arterial pressure (MAP) in the total sample (obese vs. normal weight: $\beta=3.71; p=0.0085$) and girls (obese vs. normal weight: $\beta=4.73; p=0.0444$). No main effect was observed for diastolic blood

pressure (DBP). Overall, our results show a clear relationship between fatness and blood pressure in children and adolescents. The relationship between fatness and CRP was examined in the NHANES sample only. There was a consistent, positive relationship between fatness and CRP in the total sample (obese vs. normal weight: $\beta=1.68$; $p=0.0000$; overweight vs. normal weight: $\beta=0.85$; $p=0.0001$), boys (obese vs. normal weight: $\beta=1.85$; $p=0.0000$; overweight vs. normal weight: $\beta=0.90$; $p=0.0006$), and girls (obese vs. normal weight: $\beta=1.36$; $p=0.0000$; overweight vs. normal weight: $\beta=0.70$; $p=0.0173$). The outcomes for the relationships between fatness and blood pressure and CRP were consistent with the literature and supported the hypotheses (1-4) for this dissertation. These results highlight the importance of addressing the growing problem of childhood and adolescent obesity. Overweight and obesity have been shown to track from childhood to adulthood (5), and with the positive relationship between fatness and these two cardiovascular risk factors, it is even more urgent that reducing fatness be a priority of those in public health and medicine.

The relationship between physical activity and blood pressure and CRP was examined in both samples and an inverse relationship was hypothesized. The inverse relationship with blood pressure was observed in the East of England Healthy Hearts Study in the total sample ($F(2, 6270)=4.553$, $p<0.05$), in girls ($F(2, 3026)=3.549$, $p<0.05$), and in subjects aged 12-18 years ($F(2, 4631)=4.703$, $p<0.05$). In the NHANES sample, the inverse relationship was only observed in analyses for DBP in the total sample (<15 minutes vs. active: $\beta=3.80$; $p=0.0110$) and girls (<15 minutes vs. active: $\beta=4.68$; $p=0.0111$), MAP in the total sample (<15 minutes vs. active: $\beta=2.58$; $p=0.0177$) and girls (<15 minutes vs. active: $\beta=3.18$; $p=0.0133$), and CRP in girls (<15 minutes vs. active: $\beta=-0.38$; $p=0.0456$). No relationship was detected in analyses for SBP or for boys. The literature regarding the influence of physical activity and cardiovascular risk factors such as

blood pressure and CRP is mixed (2, 6-8). While the NHANES sample had an objective measure of physical activity (accelerometry), similar results were seen in the East of England Healthy Hearts Study, which used a self-report measure of physical activity. Currently there are no child-specific cut points for adverse CRP. Thus, an understanding of the progression of CRP during childhood (independent of fatness) needs to be examined to fully understand how physical activity might influence it.

A combined association of fatness and physical activity with blood pressure and CRP was hypothesized for both samples. No combined association of fatness and physical activity with blood pressure was observed in the East of England Healthy Hearts Study. While it is possible that this combined relationship does not exist, there are other factors that may have influenced our negative finding. The sample had a lower prevalence of overweight and obesity than UK national averages (28.4% vs. 32%), which may have influenced any combined associations (interactions). Factors that could also have an influence on the combined association of fatness and physical activity, including diet, family history, and prenatal data, were not examined in this study. The heritability of blood pressure has been shown to be between 30-50% (9) and diet, the other major behavioral risk factor for CVD, can have both a positive (10-12) and negative (13-15) influence on blood pressure, depending on which aspects of diet are considered.

In contrast to the East of England study, the NHANES sample showed a combined association between fatness and physical activity with blood pressure and CRP. The association was observed for SBP in the total sample (Wald $F=204.60$; $p=0.0000$), boys (Wald $F=85.85$; $p=0.0000$), and girls (Wald $F=89.14$; $p=0.0000$), DBP in the total sample (Wald $F=18.68$; $p=0.0167$), and girls (Wald $F=17.90$; $p=0.0220$), MAP in the total sample (Wald $F=36.32$; $p=0.0000$), and girls (Wald $F=28.08$; $p=0.0005$), and CRP in the total sample (Wald $F=606.30$;

$p=0.0000$), boys (Wald $F=283.57$; $p=0.0000$), and girls (Wald $F=327.75$; $p=0.0000$). These outcomes are novel and highlight the importance of both fatness and physical activity in combating cardiovascular risk factors in children and adolescents. In previous research, this association has been observed with aerobic fitness and fatness, though the results of this study highlight that lower levels of physical activity, not just higher intensity activity, is beneficial. The use of an objective measure of physical activity strengthened our results and may have contributed to the significant association (interaction). The influence of diet and other environmental and genetic factors were not evaluated in this analysis. How these factors influence the combined association between fatness and physical activity is unknown and is important to consider in future research.

Age and gender were also examined in this dissertation as both have been shown to influence blood pressure and CRP (16-18). In the East of England Healthy Hearts Study, adequate sample size was available to allow examination of both age and gender. In boys, being in the older age category (12-18 years) increased the risk of having high normal blood pressure (OR = 1.68, CI=1.32-2.14) and hypertension (OR = 1.48, CI=1.09-2.01). In girls, being in the older age category only increased the risk of having high normal blood pressure (OR = 1.29, CI=1.02-1.64). MAP was significantly lower in boys in the 12-18 year old category when compared with boys in the 8-11 year old category, and girls had significantly higher MAP in both the younger group and the older group compared to boys in the same age category. These findings are in contrast to previous studies (19, 20), which have shown boys having higher blood pressure than girls and that blood pressure increases with age. In the NHANES sample, age categories were not formed due to the complex sampling strategy used to create a representative sample of the US population. Gender differences were examined, and boys had a significantly

higher mean systolic blood pressure (4mmHg) than girls, while they had a significantly lower (2mmHg) diastolic blood pressure than girls. No significant difference in MAP was evident as the differences in SBP and DBP likely washed out any difference that would have been seen in MAP. There was no measure of maturation in either sample, which was a limitation of both analyses. The maturation status of these children and adolescents could influence the results and could be masking any true differences between the genders and age categories. Future research should include a measure of maturation to better understand this relationship.

Of all variables considered in this study, fatness was found to be the main influence on both blood pressure and CRP in children and adolescents age 8-18 years. Physical activity was shown to influence blood pressure and CRP, though less consistently. The combined association of fatness and physical activity, while only seen in the NHANES sample, is a relationship that needs to be evaluated further and one that highlights the importance of reducing fatness and increasing the daily level of physical activity in which children and adolescents engage. Based on our results, the focus of primary care programs and interventions focused on reducing CVD risk factors should be on weight management. A reduction in body fatness will have the greatest impact on risk factors such as high blood pressure and elevated CRP, as shown from the results of these analyses. Reduction of weight can be achieved partially through the inclusion of regular daily physical activity. The low prevalence of children and adolescents meeting physical activity guidelines is a concern. Future research on the combined association of physical activity and fatness, and other potential determinants such as sleep, screen time, diet, and maternal status is warranted.

Recommendations for Future Studies:

- Examine the combined association of fatness and physical activity in a cohort of children and adolescents with high-normal blood pressure or hypertension or an elevated CRP level.
- Longitudinally assess the impact of regular physical activity on overweight and obese children and adolescents to better understand the impact on the progression of cardiovascular disease risk factors.
- Examine physical activity intensity (moderate versus vigorous) and its impact on the relationship between physical activity and blood pressure and CRP in addition to exploring the effects of sedentary behavior.
- Examine the threshold of physical activity needed to attenuate blood pressure and elevated CRP in overweight and obese children.

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