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Examining Racial Differences in Sympathetic Activity Assessed During Recovery from Exercise in Obese Adolescent Females

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Virginia Commonwealth University

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Examining Racial Differences in Sympathetic Activity Assessed During Recovery from
Exercise in Obese Female Adolescents

A thesis submitted in partial fulfillment of the requirements for the degree of Master of
Human Movement Sciences at Virginia Commonwealth University.

by

Stacey Lewis Hall
B.S., Virginia Commonwealth University, 2009

Director: R. Lee Franco, Ph.D.
Department of Health and Movement Sciences

Virginia Commonwealth University
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List of Abbreviations

% FAT	Percent Body Fat
ANS	Autonomic Nervous System
BIA	Bioelectrical Impedance Analysis
BMI	Body Mass Index
BP	Blood Pressure
BPM	Beats per Minute
CHD	Coronary Heart Disease
CVD	Cardiovascular Disease
CVF	Cardiovascular Fitness
E	Epinephrine
ERI	Exercise Recovery Index
FFM	Fat-Free Mass
HDL	High-Density Lipoprotein
HOMA-IR	Homeostasis Model Assessment for Insulin Resistance
HR	Heart Rate
HRR	Heart Rate Recovery
HRV	Heart Rate Variability
IR	Insulin Resistance
LDL	Low-Density Lipoprotein

MetS	Metabolic Syndrome
MPH	Miles per Hour
NW	Normal Weight
OB	Obese
OBSA	Obstructive Sleep Apnea
OGTT	Oral Glucose Tolerance Test
OW	Overweight
PNS	Parasympathetic Nervous System
RER	Respiratory Exchange Ratio
SA	Sinoatrial
SBP	Systolic Blood Pressure
SNS	Sympathetic Nervous System
SO	Sympathetic Overactivity
T2DM	Type II Diabetes Mellitus
TAG	Triglycerides
TC	Total Cholesterol
VO_2	Oxygen Consumption
VO_{2FFM}	Peak Oxygen Consumption per Fat-Free Mass
WC	Waist Circumference

Abstract

EXAMINING RACIAL DIFFERENCES IN SYMPATHETIC ACTIVITY ASSESSED
DURING RECOVERY FROM EXERCISE IN OBESE ADOLESCENTS

By Stacey L. Hall, M.S.

A thesis submitted in partial fulfillment of the requirements for the degree of Master of
Human Movement Sciences at Virginia Commonwealth University.

Virginia Commonwealth University, 2012.

Director: R. Lee Franco, Ph.D.
Department of Health and Movement Sciences

Sympathetic overactivity (SO) is associated with obesity and cardiovascular disease

(CVD) mortality. Black adolescents have an increased risk of obesity and CVD later in

life, particularly females. **PURPOSE**: To evaluate differences in SO between black

(BOA) and white obese female adolescents (WOA). **METHODS**: Sixty-one BOA

(n=49, 13.7 ± 1.6 yrs, 38.1 ± 6.1 kg/m^2) and WOA (n=12, 13.3 ± 2.2 yrs, 34.3 ± 4.9 kg/m^2)

completed a maximal graded treadmill test after which an exercise recovery index (ERI;

heart rate/VO$_2$ plateau) was calculated. **RESULTS**: The ERI was significantly greater in

BOA compared to WOA (29.8 ± 6.4 vs. 24.1 ± 3.1, $P = 0.004$). Multiple linear regression

modeling revealed a significant independent association between ERI and VO$_{2FFM}$ ($r = -

0.310$, $P = 0.027$) and %FAT ($r = 0.326$, $P = 0.020$) in BOA only. **CONCLUSIONS**:

These results suggest that BOA females have greater SO than WOA females.

Review of Related Literature

The metabolic syndrome (MetS), originally termed "syndrome X", is a collection of interrelated metabolic factors that concomitantly raise an individual's risk for developing coronary heart disease (CHD) and type 2 diabetes mellitus (T2DM) (Reaven,1988). According to the National Cholesterol Education Program's Adult Treatment Panel III (ATP III), MetS is identified when an individual expresses at least three of the following criteria: (1) Abdominal obesity defined by a waist circumference exceeding 102 or 88 cm for men and women, respectively, (2) Triglyceride levels greater than or equal to 150 mg/dL, (3) HDL cholesterol less than 40 or 50 mg/dL for men and women, respectively, (4) Blood pressure values greater than or equal to 130 mmHg systolic or 85 mmHg diastolic, and (5) Fasting plasma glucose levels greater than or equal to 110 mg/dL. Additionally, individuals taking anti-hypertensive or anti-diabetic medications are considered to have met the criteria for abnormal blood pressure or fasting plasma glucose, respectively (National Cholesterol Education Program [NCEP] Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults Adult Treatment Panel III [ATP III], 2002).

A single consistent and objective set of criteria for appropriately diagnosing MetS in youth has not been officially accepted in the literature. Several different MetS criteria have been employed for this population which typically involves the use of cut-points based on age- and gender-specific percentile values (Varda & Gregoric, 2009). Perhaps the most commonly used

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standards were established by Cook et al. in 2003 and define MetS in the child or adolescent when at least three of the following criteria are expressed: (1) Abdominal obesity defined by a waist circumference greater than or equal to the 90th percentile for age and gender, (2) Triglyceride levels greater than or equal to 110 mg/dl, (3) HDL cholesterol less than 40 mg/dl, (4) A systolic or diastolic blood pressure value greater than or equal to the 90th percentile for age, height, and gender, and (5) Fasting plasma glucose levels greater than or equal to 100 mg/dl (Cook, Weitzman, Auinger, Nguyen, & Dietz, 2003). Based on this definition, the prevalence for adolescent MetS in North America was most recently found to be 8.6% overall and 27.0% among obese adolescents. As a subgroup of the population studied, males had higher prevalence rates when compared to females, 10.8% and 6.1%, respectively. Furthermore, ethnicity impacts the prevalence of MetS with Hispanic and White adolescents having higher rates than Black adolescents, 11.2%, 8.9%, and 4.0%, respectively (Johnson, Kroon, Greenway, Bouchard, Ryan, & Katzmarzyk, 2009).

The pediatric MetS definition mentioned above provides a useful tool for identifying individuals who display unfavorable risk factor profiles associated with the development of diseases in adulthood (Morrison, Friedman, Wang, & Gleuck, 2008). A 25- to 30-year prospective follow-up of students participating in the Princeton Lipids Research Study revealed that pediatric MetS was an independent predictor of adult MetS and T2DM. Furthermore, adult MetS was strongly associated with changes in age-specific BMI percentile, such that for every 10-percentile unit change, the risk of adult MetS increased by 25.0% (Morrison, Friedman, Wang, & Gleuck, 2008). An increase in the degree of insulin resistance (IR) has also been shown to increase the risk of developing MetS and the prevalence of each MetS component among obese children and adolescents (Juarez-Lopez, Klunder-Klunder, Medina-Bravo,

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Madrigal-Azcarate, Mass-Diaz, & Flores-Huerta, 2010). Together these findings emphasize the central role of obesity and IR in this constellation of risk factors known as MetS. Therefore, this review will focus on obesity and IR as central components in the development of MetS and their unique role in the disruption of the autonomic nervous system (ANS), often observed in those with CVD and T2DM.

OBESITY

The World Health Organization defines obesity as the accumulation of excess body fat resulting in an increased risk for metabolic and cardiovascular complications (World Health Organization Technical Consultation, 2000). In 1998, the National Heart, Lung, and Blood Institute published clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults (National Institutes of Health, National Heart, Lung, and Blood Institute, 1998). These guidelines included body mass index (BMI), a ratio of weight (kg) relative to height squared (m^2), as a measure to quantify overweight and obesity through strong correlations with adiposity. Individuals are placed in 1 of 6 categories based on specified cut-off points representative of under-weight (<18.5 kg/ m^2), normal-weight (18.5-24.9 kg/ m^2), over-weight (25.0-29.9 kg/ m^2), or obese class I (30.0-34.9 kg/ m^2), II (35.0-39.9 kg/ m^2), or III (>40.0 kg/ m^2). In addition to BMI, waist circumference measurement (WC) is also suggested for the evaluation of disease risk. WC measures greater than 102 and 88 centimeters, for men and women respectively, place individuals at increased risk for developing obesity related CVD risk factors and morbidity (National Institutes of Health, National Heart, Lung, and Blood Institute, 1998).

In children and adolescents the BMI changes markedly with age and gender and therefore is typically considered as "BMI for age" values and interpreted using percentile cut-offs in

reference to the population (Must & Anderson, 2006). Using age- and gender-specific BMI percentile values, children and adolescents are considered obese at or greater than the 95th percentile and considered overweight lower than the 95th percentile but greater than or equal to the 85th percentile (Krebs, Hines, Jacobson, Nicklas, Guilday, & Styne, 2007). Waist circumference age-percentile scores based on population norms are an additional tool for the diagnosis of child and adolescent overweight and obesity (Reilly, 2010). A recent systematic review showed similar accuracy for the BMI and waist circumference techniques in diagnosing obesity and risk for adverse cardiovascular risk factors (Reilly, Kelly, & Wilson, 2010).

According to most recent prevalence estimates, 18.1% of U.S. adolescents ages 12-19 years are considered obese based on BMI for age values. Furthermore, ethnicity and gender play a role in the distribution of obesity across the population with black adolescent females having higher prevalence rates than white or Hispanic adolescent females, 29.2%, 14.5%, and 17.5%, respectively (Ogden, Carrol, Curtin, Lamb, & Flegal, 2010). Obesity in this age group is associated with an increased risk for obesity and all-cause mortality in adulthood (McTigue, Garrett, & Popkin, 2002). The ethnic differences seen in adolescent prevalence rates extends into adulthood as approximately 54.0% of U.S. black women and 30.0% of white women are considered obese (Ogden, Carroll, Curtin, McDowell, Tabak, & Flegal, 2006). Together these findings suggest a racial divergence in the pathogenesis of obesity (Srinivasan, Myers, & Berenson, 2001).

Pathophysiological mechanisms related to poor cardiovascular outcomes in adults are already operative in obese adolescents. The degree of obesity in adolescence is a clinically relevant predictor of cardiovascular risk such that worsening BMI negatively effects the expression of each MetS component, namely IR (Weiss et al., 2004). The patterning of fat across

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visceral and subcutaneous depots further describes these metabolic consequences such that adolescents with greater visceral accumulations express significantly higher IR, plasma triglyceride levels, and lower HDL concentrations (Taksali, 2008). Ethnicity also plays a role in the expression of metabolic consequences associated with being obese. A multi-ethnic study examining CVD risk profile in obese black and white female adolescents revealed that despite similar BMI, total body fat, and percent body fat, black subjects had nearly 30.0% less visceral adipose tissue than their white peers. Interestingly, when these variations were related to metabolic parameters such as lipid profile and IR, a more atherogenic risk profile was observed in whites whereas blacks appear to display a more diabetogenic (insulin resistant) profile (Bacha, Saad, Gungor, Janosky, & Arslanian, 2003).

INSULIN RESISTANCE

Under normal conditions, beta cells of the human pancreas secrete the hormone insulin, which is responsible for regulating the metabolism of glucose, lipids, and proteins, as well as maintaining blood glucose concentrations (~ 80-90mg/100ml fasting state). Insulin is released in response to the ingestion of high energy yielding meals and results in a shift from resting fatty acid utilization to the rapid uptake, storage, and use of glucose by all the tissues of the body, namely the liver, adipose tissue, and muscle cells. These tissues convert any excess glucose into its storage form, glycogen, which can later be used for energy by the muscles when necessary. Between meals, when blood glucose concentrations begin to fall, insulin secretion is decreased and the stored liver glycogen is broken down to glucose and released into the blood stream (Guyton & Hall, pp. 961-965).

The assessment of insulin action commonly employs measures that reflect the sensitivity of insulin to promote glucose uptake by the tissues and its subsequent metabolism. Insulin

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sensitivity can be assessed through direct and indirect methods, both of which measure the status of glucose metabolism in either stable or unstable circumstances (Matsuda, 2010). To fully understand the mechanisms through which abnormalities in glucose handling cultivate, it is necessary to assess the action of multiple physiological variables, primarily, the pancreatic beta-cell response to a given glucose load and the sensitivity of the tissues to insulin. Because the processes involved in glucose homeostasis at both the tissue and beta-cell level occur simultaneously rather than in a specific sequence, an optimal measure of insulin resistance would involve in vivo methods to assess both beta-cell sensitivity to glucose and tissue sensitivity to insulin. For this, the glucose clamp technique, proposed by DeFronzo and colleagues in 1979, provides a highly reproducible method (DeFronzo, Tobin, & Andres, 1979).

The glucose clamp technique is considered the gold standard measure of insulin action (Ferrannini & Mari, 1998). The clamp technique can be performed through two different versions, involving euglycemic or hyperglycemic methods as outlined by DeFronzo et al. (DeFronzo, Tobin, & Andres, 1979). These methods provide reliable measures to quantify both beta-cell function and the sensitivity of insulin to act on its target tissues. However, these methods present several disadvantages. The requirement for two intravenous lines, calibrated pumps, and trained personnel make these techniques less practical for the widespread clinical diagnoses of IR. For this reason, simpler methods are more practical for use outside of specialized research clinics (Ferrannini & Mari, 1998).

The most common measure used to quantify whole body glucose tolerance in vivo is the oral glucose tolerance test (OGTT). Aside from its use in quantifying glucose tolerance, the OGTT provides the ability to reflect the effectiveness of the beta-cells and the sensitivity of the tissues to insulin with reasonable accuracy when compared to the previously described clamping

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techniques (Stumvoll et al., 2000). Generally, the OGTT is administered following an overnight fast of at least 10 hours, no less than three days of an unrestricted diet (>150 g of carbohydrate per day), and normal physical activity. Fasting blood samples are drawn to measure plasma glucose and insulin concentrations after which the subject is asked to ingest a solution containing 75g of glucose in 250-300 ml of water within a 5 minute time period. Following the ingested glucose load, blood samples are taken every half hour for a total of 2 hours to assess plasma glucose and insulin levels (World Health Organization Expert Committee on Diabetes Mellitus, 1980). The blood glucose samples retrieved during an OGTT are used to stratify individuals into three categories of glucose tolerance based on 2-hour postload glucose values. Glucose values less than 140 mg/dl represent normal glucose tolerance, while any value between 140mg/dl and 199 mg/dl represents impaired glucose tolerance. Blood glucose values greater than 200 mg/dl represent a provisional diagnosis of diabetes (American Diabetes Association, 2009).

The homeostasis model assessment of insulin resistance (HOMA-IR) provides a simple and inexpensive alternative to the aforementioned techniques for assessing insulin sensitivity. HOMA-IR was developed in 1985 by Mathews et al. (Matthews, Hosker, Rudenski, Naylor, Treacher, & Turner, 1985) with the use of computer aided modeling of experimental human and animal data. To compute HOMA-IR, a simple mathematical approximation is employed using the product of fasting insulin and glucose values [HOMA-IR = fasting plasma glucose (mmol/L) x fasting plasma insulin (µU/ml)/22.5] (Matthews, Hosker, Rudenski, Naylor, Treacher, & Turner, 1985). The estimate of IR derived from HOMA-IR is significantly correlated to the gold-standard clamp techniques ($R_s = 0.88$, $P < 0.0001$) (Matthews, Hosker, Rudenski, Naylor, Treacher, & Turner, 1985), ($R_s = 0.85$, $P < 0.0001$) (Bonora et al., 2000).

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The inability of insulin to stimulate its numerous functions, including the homeostasis of blood glucose, despite normal production and secretion of insulin by the pancreas, describes the pathological state of IR (Reaven, 1988). In this compromised metabolic state, the beta cells of the pancreas are stimulated to secrete higher than normal concentrations of insulin in an attempt to maintain normal blood glucose levels. The resulting compensatory hyperinsulinemic state is associated with glucose intolerance, increased plasma triglycerides, and decreased high-density lipoprotein cholesterol, all of which contribute to increased CHD mortality and overall cardiovascular risk (Fontbonne & Eschwege, 1991). Furthermore, it is generally accepted that IR is a primary contributor toward the development of T2DM (DeFronzo, Bonadonna, & Ferrannini, 1992).

The body's attempt to compensate for IR triggers a cascade of events that are pivotal in the development of hypertension, T2DM, coronary artery disease, and MetS (Reaven, 1988). In 1988, these events led Dr. Gerald M. Reaven to first propose the suggestion that IR plays a primary role in the development of MetS (Reaven, 1988). A general consensus now exists regarding the role of IR as a pathophysiological trait of MetS, however the central cause of IR is a highly debated topic (Savage, Petersen, & Shulman, 2005). Although exact mechanisms remain to be established, IR is thought to originate primarily through a genetic abnormality or obesity (Mitchell et al., 1996).

Differences in insulin secretion and sensitivity across ethnicities have been reported in healthy and obese adolescents. In healthy adolescents, responses to a 2-hour hyperglycemic clamp were examined in 14 black and 16 white subjects. First and second phase insulin concentrations were significantly higher in blacks compared to whites. Additionally, an insulin sensitivity index was 35% lower in black adolescents compared with whites ($P = 0.02$) indicating

ethnic differences in insulin secretion and sensitivity early in life, even in healthy individuals (Arslanian, 1998). Guitin et al., examined the role of fatness and fitness in describing the variation in fasting insulin concentrations amongst adolescents (Guitin, Yin, Humphries, Hoffman, Gower, & Barbeau, 2004). Both cardiovascular fitness and percent body fat explained significant proportions of the variance in fasting insulin concentration with higher partial R^2 values for fatness ($R^2 = 0.33$; $P < 0.0001$) than for fitness ($R^2 = 0.17$; $P < 0.0001$). In this group of adolescents, blacks displayed significantly higher fasting insulin values than whites, especially in females (Guitin, Yin, Humphries, Hoffman, Gower, & Barbeau, 2004).

Regardless of age or gender, the degree of IR is associated with a higher prevalence of disorders related to each component of MetS in obese adolescents (Juarez-Lopez, Klunder-Klunder, Medina-Bravo, Madrigal-Azcarate, Mass-Diaz, & Flores-Huerta, 2010). Recent research has suggested a link between dysfunction of the ANS, obesity, and/or obesity-related disorders (Scherrer, Randlin, Tappy, Vollenweider, Jequier, & Nicod, 1994; Grassi et al., 1995). Altered ANS function, such as an attenuated parasympathetic nervous system (PNS) and/or an overactive sympathetic nervous system (SNS), has been demonstrated in patients with hypertension, MetS, obesity, and IR (Curtis & O'Keefe, 2002).

THE AUTONOMIC NERVOUS SYSTEM

The ANS is important in maintaining homeostasis of the human body and in performing various functions responsible for regulating the cardiovascular system in both healthy and diseased populations. The primary task of the ANS involves conveying impulses from the central nervous system to peripheral organs. The ANS is composed of two branches, the PNS and SNS. Collectively these two branches work in synchrony to control HR, constriction and

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dilation of blood vessels, contraction and relaxation of smooth muscle in a number of organs, and various glandular secretions (Freeman, Dewey, Hadley, Myers, & Froelicher, 2006).

The PNS, known for its role during resting conditions, is primarily responsible for conserving energy by reducing HR and blood pressure. This arm of the ANS is also known for facilitating digestion and absorption of nutrients (Freeman, Dewey, Hadley, Myers, & Froelicher, 2006). Approximately 75 percent of PNS innervation is supplied through the vagus nerve, which controls the entire thoracic and abdominal regions of the body including the heart, lungs, esophagus, stomach, liver, pancreas, and kidneys. Virtually all of the terminal nerve endings of the PNS secrete the neurotransmitter acetylcholine (Ach). Therefore, these PNS post-ganglionic neurons are termed cholinergic (Guyton, pp. 750-751).

Opposing the actions of the PNS, the SNS prepares the body for challenges to survival (fight or flight) by a.) increasing HR, BP, and cardiac output, b.) diverting blood flow from the organs and skin to the skeletal muscles, c.) dilating the bronchioles in the lungs, and d.) reducing metabolic activity (Freeman, Dewey, Hadley, Myers, & Froelicher, 2006). Nearly all of the sympathetic nerve endings respond to adrenal secretion of the neurotransmitters epinephrine (E) and norepinepherine (NE), otherwise known as adrenalin and noradrenalin, respectively. Because sympathetic responses are mediated through adrenalin and noradrenalin, SNS post-ganglionic neurons are termed adrenergic (Guyton, p. 750-751).

At rest, the sinoatrial (SA) node of the heart is responsible for controlling myocardial contraction rate. The SA node is controlled by an intrinsic rate of spontaneous depolarization in the absence of influences from the ANS, referred to as the intrinsic HR (Jose & Collison, 1970). The intrinsic HR is approximately 100 beats per minute (bpm) in healthy humans and is dependent upon age, gender (Jose & Collison, 1970), and fitness status of an individual (Katona,

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McLean, Dighton, & Guz, 1982). SNS and PNS stimulation of the SA node predominates over the intrinsic HR such that PNS stimulation acts to slow HR whereas SNS activation accelerates HR (Scher, Ohm, Bumgarner, Boynton, & Young, 1972).

The ANS regulates HR at the onset, during, and following dynamic exercise. At the onset of exercise, HR increases rapidly followed by more gradual elevations in response to increasing workloads (Goldsmith, Bloomfield, & Rosenwinkel, 2000). Maciel et al. evaluated the participation of both branches of the ANS within the initial HR response to dynamic exercise (Maciel, Gallo, Marin Neto, Lima Filho, & Martins, 1986). PNS and SNS inhibition was achieved through intravenous administration of atropine and propranolol, respectively. Restriction of the PNS abolished the initial rapid increase in HR during the first 10 seconds. However, when the SNS was restricted there was no effect on HR during this same time period. During the slow phase of HR elevation, between 1 to 4 minutes of exercise, SNS restriction resulted in a significantly depressed HR response. These results suggested that the rapid HR response to exercise is initially mediated by PNS withdrawal, up to approximately 100 beats per minute (bpm), and the latter more gradual HR response is managed by SNS stimulation, occurring at HR values greater than 100 bpm (Maciel, Gallo, Marin Neto, Lima Filho, & Martins, 1986).

Autonomic control of HR during exercise has been shown to vary in response to the relative intensity of the exercise bout (Maciel, Gallo, Marin Neto, Lima Filho, & Martins, 1986). The acceleration of HR throughout exercise appears to occur in response to PNS withdrawal during relatively mild intensities (Robinson, Epstein, Beiser, & Braunwald, 1966). However, heightened SNS activity becomes progressively more important as the intensity of exercise increases up to maximal levels (Robinson, Epstein, Beiser, & Braunwald, 1966). Due to the

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effects of progressive workload on autonomic stimulation, the intensity of an exercise bout will determine the speed at which HR returns to basal levels upon cessation of exercise (Savin, Davidson, & Haskell, 1982).

Immediately following a dynamic exercise bout, HR decelerates exponentially toward resting values, a condition which is mediated through ANS control of the heart. The time course and particular contributions of each branch of the ANS to HR deceleration during recovery from exercise has been assessed in athletes, patients with heart failure, and normal subjects (Imai et al., 1994). Among athletes and normal subjects, there was a steep decline in HR during the first 30 seconds of recovery followed by a more shallow decline throughout the remainder of the 2 minute recovery period. Upon administration of atropine for PNS blockade, the initial steep decline was abolished. Based on these results the authors concluded that early heart rate recovery (HRR) is mediated by PNS reactivation (Imai et al., 1994). Late HRR is said to be mediated by withdrawal of SNS stimulation, especially following high intensity exercise (Kannankeril, Le, Kadish, & Goldberger, 2004).

ANS balance can be demonstrated by evaluating cardiopulmonary responses to various stimuli including plasma neurotransmitter concentrations, muscle sympathetic nerve activity, HR, heart rate variability (HRV), and HRR (Freeman, Dewey, Hadley, Myers, & Froelicher, 2006). All of these measures are strong predictors of cardiovascular risk and all-cause mortality (Lahiri, Kannankeril, & Goldberger, 2008). However, no measure provides a valid assessment of ANS function under all conditions. Therefore, when possible, it is advantageous to employ multiple techniques (Snitker, Macdonald, Ravussin, & Astrup, 2000).

HRR provides important prognostic value to exercise testing. Attenuated HRR following maximal exercise is an independent predictor of all-cause mortality in adults (Cole, Blackstone,

Pashkow, Snader, & Lauer, 1999). Lin et al. tested this relationship in adolescents using HRR at 1, 2, and 3 minutes post-exercise (1-, 2-, and 3-min HRR, respectively). Significant inverse associations were observed between the HRR parameters and metabolic risk factors including waist circumference ($P = 0.001$ and <0.0001 for 2- and 3-min HRR, respectively), SBP ($P = 0.029$ for 1-min HRR), and fasting glucose ($P = 0.021$ for 2-min HRR).   Additionally, the correlation between metabolic risk as a whole and 2- and 3-min HRR was significantly stronger in females than in males (Lin, Kuo, Lai, Lin, Tseng, & Hwang, 2008).

Yeckel et al. recently introduced a novel exercise recovery index as a minimally invasive method to indirectly assess health status in respect to fitness, ANS control, and level of IR in at-risk young individuals (Yeckel, Gulanski, Zgorski, Dziura, Parish, & Sherwin, 2009). By extending the HRR period from a maximal exercise test beyond the initial rapid PNS response (~ 2 minutes), the investigators found the degree of heart rate recovery normalized for oxygen consumption (HR/VO$_2$ plat) to provide a functional index of sympathetic activity. Furthermore, HR/VO$_2$ plat was significantly associated with basal IR as well as stimulated whole-body insulin sensitivity affording this tool unique utility when exploring ANS function related to diseases associated with obesity and IR (Yeckel, Gulanski, Zgorski, Dziura, Parish, & Sherwin, 2009).

Cardiovascular ANS function in adolescents has been explored in response to short-term evoked cardiovascular autonomic reactivity tests (Faulkner, Hathaway, & Tolley, 2003), urinary and plasma catecholamine levels (Wambach, Hossmann, Bonner, & Laaser, 1986), as well as short-term and 24-hour HRV recordings (Tanaka, Borres, Thulesius, Tamai, Ericson, & Lindblad, 2000). Evidence suggests that healthy black adolescents display significantly higher cardiovascular ANS function, as compared to healthy white adolescents (Li et al., 2009; Gutin, Howe, Johnson, Humphries, Snieder, & Barbeau, 2005; Wang, Thayer, Treiber, & Snieder,

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2005; Urbina, Bao, Pickoff, & Berenson, 1998). In particular, Gutin et al. revealed more favorable ANS profiles in healthy black adolescents than in whites, despite higher SBP values in blacks. Interestingly, the deleterious effects of poor body composition on ANS function were only significant in blacks, particularly females. These findings suggest that as weight gain ensues, cardiac ANS function is compromised to a greater extent in black female adolescents than black male or white adolescents (Gutin, Howe, Johnson, Humphries, Snieder, & Barbeau, 2005).

ANS FUNCTION, INSULIN RESISTANCE & OBESITY IN ADOLESCENCE

Abnormalities in SNS activity are often observed in individuals who express components of MetS, either individually or collectively. More specifically, attention has shifted toward the role of SNS activity in the development and progression of obesity, however whether abnormal SNS activity causes or is a consequence of obesity remains unresolved. Obesity is not an entirely homogenous disorder given that both SNS over- and under-activation have been documented in its presence (Snitker, Macdonald, Ravussin, & Astrup, 2000). Blunted SNS activity has been implicated in the genesis of obesity as a result of deficient thermogenesis eventually leading to a positive energy balance and thus weight gain (Bray, 1991). On the other hand, SNS overactivation, which specifically targets the heart, blood vessels, and kidneys, appears to exacerbate the metabolic consequences associated with obesity by predisposing individuals to the development of hypertension and other CVD risk factors (Davy & Hall, 2004).

The relationship between ANS modulation and metabolic characteristics in obese children and adolescents has received increasing attention over the past decade. As similarly observed in an adult population, equivocal data between the communicative exchange of the two ANS branches in obese adolescent individuals has revealed both over- (Riva et al., 2001; Rabbia

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et al., 2003; Tascilar, Yokusoglu, Boyraz, Baysan, Koz, & Dundaroz, 2011) and under-activation (Yakinci, Mungen, Karabiber, Tayfun, & Evereklioglu, 2000; Vanderlei, Pastre, Junior, & Godoy, 2010; Dangardt, Volkmann, Chen, Osika, Marild, & Friberg, 2011) of the SNS. The conflicting results could be related to the difficulty in controlling several variables in obese adolescents, such as IR, hypertension, and ethnicity (Nagai, Matsumoto, Kita, & Moritani, 2003).

To describe the metabolic and ANS phenotype in adolescent obesity, Rabbone et al. examined the relationship between indices of insulin sensitivity and beta-cell function in relation to cardiac ANS regulation (Rabbone et al., 2009). Eighteen female obese adolescents (12.7 ± 0.2 years) and ten lean age- and gender-matched controls completed an OGTT for the estimation of insulin sensitivity and beta-cell function and 24-hour ECG Holter and ambulatory BP monitoring for the assessment of ANS function. Adolescent obesity was characterized by ANS imbalance reflecting a significant reduction in PNS activation ($P < 0.05$) and subsequent elevation in SNS activation, which failed to reach significance. PNS parameters were inversely related to insulin sensitivity indices ($P < 0.05$) but not with insulin secretion. In accord with the relationship between ANS function and CVD risk factors such as IR, the evaluation of ANS pattern can be considered a useful tool in evaluating the early cardiovascular impact of weight gain in young populations (Rabbone et al., 2009).

Cardiac ANS function and metabolic characteristics, namely IR, were evaluated in 32 obese children (11.6 ± 2 years) and 30 age- and gender-matched control subjects (Tascilar, Yokusoglu, Boyraz, Baysan, Koz, & Dundaroz, 2011). Time- and frequency-domain parameters of HRV were assessed using 24-hour ambulatory electrocardiographic recordings and level of IR was assessed with the HOMA-IR technique. All HRV parameters, with the exception of SDNN, were significantly reduced ($P < 0.022$) in obese children, reflecting PNS withdrawal and SNS

dominance. Concerning metabolic status, the obese group had significantly higher insulin, triglycerides, vLDL-cholesterol, and lower HDL-cholesterol than controls. Interestingly, when compared to their non-insulin-resistant counterparts, insulin-resistant obese children demonstrated markedly higher SNS dominance (P = 0.007) (Tascilar, Yokusoglu, Boyraz, Baysan, Koz, & Dundaroz, 2011).

Kaufman et al. aimed to further elucidate the differences in ANS function between normal-weight (NW), overweight (OW), and obese (OB) children (11.5 ± 0.8 years) and the relationships between ANS function, leptin, and IR in each group (Kaufman, Kaiser, Steinberger, Kelly, & Dengel, 2007). 36 children (18 male, 18 female) were defined as NW, OW, or OB by an age-adjusted BMI score of less than the 85th percentile, between the 85th and 95th percentiles, and greater than the 95th percentile, respectively. OB children had significantly higher HRV markers of SNS activity (P = 0.001) and significantly lower PNS activity (P = 0.001). No apparent differences were observed between OW and NW groups for either of the HRV measures of ANS function. A significant positive association was observed between SNS dominance and IR (r = 0.34, P < 0.05). This association vanished when adjusted for fat mass (r = -0.01, P = NS) suggesting a primary role of adiposity in this relationship (Kaufman, Kaiser, Steinberger, Kelly, & Dengel, 2007).

In adults, obesity and hypertension are more common in blacks than in whites (Dustan, 1990). When considering gender with race, the prevalence of both obesity and hypertension is higher in black women than white women. In men, no racial differences exist in obesity however black men display higher prevalence rates of hypertension when compared to white men (Liu et al., 1993). SNS overactivity is a common hallmark of the obese state and thus has been implicated as a link between obesity and hypertension in black Americans (Eslami & Tuck,

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2003). To determine whether obesity causes SNS overactivity in black Americans Abate et al. recorded muscle sympathetic nerve discharge in 92 normotensive black men and women with a wide range of BMI (Abate et al., 2001). In black women, overweight was closely correlated to SNS dominance ($r = 0.45$, $P = 0.0009$) whereas in black men SNS activity was dissociated from BMI ($r = 0.03$, $P = $ NS) (Abate et al., 2001). These ethnic and gender differences in SNS function were further supported by the same group of investigators who found that dietary-induced weight loss expressed a significant positive effect on muscle SNS activity in black women ($P = 0.03$) but not in black men (Abbas et al., 2010).

As detailed throughout this review, black individuals are at an increased risk of obesity, IR, and cardiovascular disease mortality during adulthood (Meadows et al., 2011). Studies have shown ethnic differences in ANS function in healthy youth (Wang, Thayer, Treiber, & Sneider, 2005) however to date, no studies have examined the effects of ethnicity on cardiovascular ANS function in obese adolescents. Therefore the primary aim of this study is to explore the relationship between ethnicity and SNS function, assessed with the exercise recovery index proposed by Yeckel et al., in an obese adolescent population. Additionally, relationships between several variables known to affect ANS control in this population, namely cardiovascular fitness, level of obesity, IR, gender, and duration of obesity will be explored. Cardiovascular health/fitness outcomes, including maximal HR and maximal oxygen consumption will be measured during a graded exercise test on a treadmill to volitional fatigue. Additionally, SBP, both at rest and in response to a graded exercise test will be measured. To assess SNS activity, HR and VO_2 will be collected simultaneously every 30 seconds during a five-minute passive recovery period. Fasting blood samples will be taken to assess insulin sensitivity through the HOMA-IR technique. Anthropometric measures will include BMI-for-age percentile values,

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waist and hip circumference-for-age percentile values, and lastly dual-energy x-ray

absorptiometry will be used to measure regional adiposity.

Ruth Kirchenstein Proposal

SPECIFIC AIMS

SA1:   The primary aim of this study is to evaluate racial differences in SNS activity, assessed
with an exercise recovery index, in obese female adolescents.

SA2:   A secondary aim is to assess the extent to which several variables known to affect ANS
control, namely cardiovascular fitness, level of obesity, IR, and duration of obesity, help explain
the variance among autonomic nervous system function in obese adolescent females of different
ethnicities.

RESEARCH STRATEGY

Significance

The metabolic syndrome (MetS), originally termed "syndrome X", is a collection of
interrelated metabolic factors that concomitantly raise an individual's risk for developing
coronary heart disease (CHD) and type 2 diabetes mellitus (T2DM) (1). MetS in the child or
adolescent is defined when at least three of the following criteria are expressed: 1). Abdominal
obesity defined by a waist circumference greater than or equal to the 90th percentile for age and
gender, 2). Triglyceride levels greater than or equal to 110 mg/dl, 3). HDL cholesterol less than
40 mg/dl, 4). A systolic or diastolic blood pressure value greater than or equal to the 90th

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percentile for age, height, and gender, and 5). Fasting plasma glucose levels greater than or equal to 100 mg/dl (2). Based on this definition, the prevalence for adolescent MetS in North America was most recently found to be 8.6% overall and 27.0% among obese adolescents (3). An increase in adiposity and the degree of insulin resistance (IR) have been shown to increase the risk of developing MetS among obese children and adolescents emphasizing the central role of obesity and IR in this constellation of risk factors (4).

The World Health Organization defines obesity as the accumulation of excess body fat resulting in an increased risk for metabolic and cardiovascular complications (5). Body mass index (BMI), a ratio of weight (kg) relative to height squared (m^2), is a measure commonly used to quantify overweight and obesity through strong correlations with adiposity (6). In children and adolescents the BMI changes markedly with age and gender and therefore is typically considered as "BMI for age" percentile values in reference to the population (7). According to most recent prevalence estimates, 18.1% of U.S. adolescents ages 12-19 years are considered obese, having BMI for age values $\geq 95^{th}$ percentile. Furthermore, in females, the impact of ethnicity plays a role in the distribution of obesity with black adolescents having higher prevalence rates than white or Hispanic adolescents, 29.2%, 14.5%, and 17.5%, respectively (8). These ethnic differences extend into adulthood as approximately 54.0% of U.S. black women compared to 30.0% of white women are considered obese (9).

It has been suggested that white adolescents demonstrate a more atherogenic risk profile whereas black adolescents appear to display a more diabetogenic (insulin resistant) profile (10). The inability of insulin to stimulate its numerous functions, including the homeostasis of blood glucose, despite normal production and secretion of insulin by the pancreas, describes the pathological state of IR. The body's attempt to compensate for IR triggers a cascade of events

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that are pivotal in the development of hypertension, T2DM, coronary artery disease, and MetS (1). Significant differences have been observed across ethnicities in analysis of insulin secretion and sensitivity in both healthy and obese adolescents. Black subjects, as compared to white subjects, have shown significantly lower sensitivity (11) and significantly higher fasting insulin concentrations (12). Regardless of age and gender, the degree of IR is often associated with a higher prevalence of disorders related to each component of MetS in obese adolescents (4). Recent research has suggested a link between dysfunction of the autonomic nervous system (ANS) and factors common to MetS, namely obesity and IR (13,14).

Black adolescents have an increased risk of obesity, IR, and cardiovascular disease mortality later in life (15). Additionally, current evidence suggests that healthy black adolescents display higher cardiovascular ANS reactivity than healthy white adolescents (16-19). A study performed by Gutin et al. revealed that the deleterious effects of poor body composition on ANS function were only significant in blacks, particularly females, suggesting that as weight gain ensues, cardiac ANS function is compromised to a greater extent in black female adolescents than black male or white adolescents (17). The relationship between ANS modulation and metabolic characteristics in obese children and adolescents has received an increase in attention over the past decade. In agreement with observations reported in adults, differing data describing the interplay between the two branches of the ANS in obese adolescents has been observed, revealing both over- (20-22) and under-activation (23-25) of the SNS. The conflicting results could be related to the difficulty in controlling several variables when measuring ANS function in this population, such as metabolic profile and ethnicity (26).

Cardiopulmonary responses to evoked cardiovascular reactivity tests, such as exercise testing, can be used to demonstrate ANS balance through evaluations of plasma neurotransmitter

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concentrations, muscle sympathetic nerve activity, heart rate, blood pressure, heart rate variability (HRV), and HRR (27). Yeckel et al. recently introduced a novel exercise recovery index as a minimally invasive method to indirectly assess health status in respect to fitness, SNS control, and level of IR in at-risk young individuals (28). By extending the HRR period from a maximal exercise test beyond the initial rapid PNS response (~ 2 minutes), the investigators found the degree of heart rate recovery normalized for oxygen consumption (HR/VO_2 plat) to provide a functional index of sympathetic activity. Furthermore, HR/VO_2 plat was significantly associated with basal IR as well as stimulated whole-body insulin sensitivity affording this tool unique utility when exploring ANS function related to diseases associated with obesity and IR (28).

To date, no studies have examined the effects of ethnicity on cardiovascular ANS function in obese adolescents. Discovering ethnic differences in ANS modulation and the relationships between the metabolic consequences of obesity distinct to each race could offer valuable insight for treatment and prevention strategies in these at-risk obese adolescents.

APPROACH

Subjects. Seventy-five obese white and black adolescent females (BMI ≥95th percentile for age and gender) will be recruited from the VCU TEENS program to participate in this study. Only individuals cleared for participation in exercise testing by the TEENS physicians will be recruited. All participants will perform a graded maximal exercise test on a treadmill to exhaustion and undergo blood sampling for metabolic testing. Subjects who have been diagnosed with any known form of cardiovascular disease or diabetes, taking any medications known to affect insulin action or autonomic function, or have any orthopedic problems limiting the ability to complete the exercise test will be excluded from the study. All subjects and

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parents/legal guardians will be familiarized with procedures and subsequently asked to sign consent and assent forms, respectively.

Graded Exercise Test. Subjects will perform a progressive maximal treadmill walking test until volitional fatigue. Resting hear rate and blood pressure will be measured prior to testing. The treadmill protocol will consist of a 4 minute warm up at 2.5 MPH at 0% grade followed by a 2 minute stage at 3.0 MPH at 0% grade. Subsequent 2 minute stages will be held at 3.0 MPH and grade will be increased by 2.5% every 2 minutes until the subject is no longer able to maintain the treadmill pace. Heart rate will be obtained at the end of every minute utilizing a heart rate monitor. Blood pressure and ratings of perceived exertion (6-20 Borg Scale) will be obtained at the end of every stage. Continuous breath by breath measurement of VO_2 (L/min^{-1} & $ml/kg/min^{-1}$), VCO_2 (L/min^{-1}), respiratory rate (breaths per minute), and RER (VCO_2/VO_2) will be obtained during the exercise test.

Assessment of Autonomic Function. Following attainment of VO_{2peak}, subjects will stop pedaling and passively cool down for 5 minutes while seated on the cycle ergometer. To assess parasympathetic nervous system activity, the decline in heart rate recovery at 1 and 2 minutes post-exercise will be evaluated. To assess sympathetic nervous system activity, HR and oxygen consumption (VO_2) will be recorded simultaneously every 30 seconds during the five-minute passive recovery period. The value representing the time point during recovery where the ratio of heart rate recovery to oxygen consumption (HR/VO_2) initially reaches a plateau will represent a functional index of sympathetic activity.

Insulin Resistance/Sensitivity. As part of their enrollment into the TEENS program, participants will have resting glucose and insulin values measured, as well as complete an oral glucose tolerance test. To compute the Homeostasis Model Assessment of Insulin Resistance (HOMA-

IR), a simple mathematical approximation will be employed using the product of fasting insulin and glucose values (HOMA-IR = [(fasting plasma glucose x fasting plasma insulin)/22.5]). The composite Whole Body Insulin Sensitivity Index (WBISI) is based on values of insulin and glucose obtained from the OGTT (WBISI = [10,000/$\sqrt{}$((fasting glucose x fasting insulin)(mean glucose x mean insulin))]).

Body Composition Assessment. Body composition will be assessed with dual-energy x-ray absorptiometry (DXA). The DXA will provide a measure of fat mass, fat-free mass and percent body fat. Additionally, abdominal girth will be measured at the level of the umbilicus. Waist circumference will be measured at the narrowest point on the torso. Hip circumference will be measured at the maximal circumference of the buttocks. Waist-to-Hip ratio will be used to help determine the degree of abdominal obesity. All measures are made using an anthropometric tape. Height will be assessed with a stadiometer (cm) and body mass (kg) will be determined with a medical scale. Body mass index (kg/ m^2) will be calculated by dividing weight (kg) by height squared (m^2).

Statistical Analyses. An analysis of variance will be performed to determine significant differences between groups. Multiple linear regression modeling will be used in order to determine relationships between the exercise recovery index with cardiorespiratory fitness, anthropometric measures, insulin resistance, gender, and duration of obesity.

PREMILINARY STUDIES

Reductions in Functional Sympathetic Overactivity in Obese Adolescents Following a Weight Management Program

Hall, SL.[1], Franco, RL.[1], Bowen, MK.[1], Stern, M.[2], Wickham, EP.[3], Evans, RK.[1].

Departments of Health and Human Performance[1], Psychology[2], and Pediatrics[3].

Virginia Commonwealth University, Richmond, VA

Abstract

Sympathetic overactivity (SO) is associated with several disease states including type 2 diabetes and obesity. **PURPOSE:** To evaluate the association of SO, as assessed by an exercise recovery index (ERI; heart rate/VO2 plateau), with insulin resistance (HOMA-IR), cardiovascular fitness (VO2peak), and percent body fat (%FAT) in obese adolescents participating in a three month weight management program. **METHODS:** Forty participants (13.7 ± 1.6 yrs.; Body Mass Index, 36.9 ± 6.5 kg/m2) volunteered to participate in this study. % FAT, VO2peak, ERI, HOMA-IR were assessed at enrollment and after 3-months of program participation. Program components included physical activity, nutrition education, and behavioral support. **RESULTS:** Using multiple linear regression modeling, there was a significant independent association between ERI and %FAT ($r = 0.539$, $p < 0.000$) after controlling for both VO2peak per lean tissue and HOMA-IR. However, VO2peak per lean tissue ($r = -0.306$, $p = 0.061$) and HOMA-IR ($r = 0.052$, $p = 0.755$) were not independently associated with ERI. ERI ($n = 23$; 29.1 ± 7.1 vs. 25.1 ± 7.6, $p = 0.027$) and VO2peak per lean tissue ($n = 23$; 47.2 ± 7.5 vs. 50.6 ± 8.2, $p = 0.023$) were significantly reduced after the program. %FAT and HOMA-IR remained unchanged. **CONCLUSIONS:** These results suggest that insulin resistance is distinct and not impacted by SO in young overweight adolescents. Additionally, involvement in a weight management program may attenuate the development of pathological risk factors associated with SO.

DEGREE SOUGHT DURING PROPOSED AWARD

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A Masters of Science (M.S.) degree in Health and Movement Science is currently in progress at Virginia Commonwealth University, Richmond, VA. Expected completion date is May, 2012.

GOALS FOR FELLOWSHIP AND TRAINING

The primary goal for my current training experience is to prepare for study in an exercise physiology doctoral program. Ultimately, I want to become an independent research scientist who is able to contribute novel findings on the relationships between metabolic characteristics expressed in obesity and their impact on autonomic function. Lastly, a long-term goal consists of directing an externally funded laboratory at a research I institution.

ACTIVITIES PLANNED UNDER AWARD

ACTIVITIES PLANNED UNDER THIS AWARD: Approximate percentage of proposed award time in activities identified below.				
Year	**Research**	**Course Work**	**Teaching**	**Clinical**
2012	100%	0%	0%	0%

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Examining Racial Differences in Sympathetic Activity Assessed During Recovery from Exercise
in Obese Adolescent Females

INTRODUCTION

Adolescent obesity has been increasing at alarming rates over the past three decades with

most recent prevalence estimates classifying 18.1% of U.S. adolescents as obese (Body Mass

Index [BMI] > 95th percentile for age and gender) (Ogden, Carrol, Curtin, Lamb, & Flegal,

2010). This rise in adolescent obesity has led to an equally alarming 8.6% prevalence of

adolescent metabolic syndrome (MetS), a clustering of metabolic abnormalities that tend to

originate from obesity (Johnson, Kroon, Greenway, Bouchard, Ryan, & Katzmarzyk, 2009).

MetS, which includes impaired glucose tolerance, hypertension, elevated triglyceride and LDL

cholesterol, and low HDL cholesterol, significantly increases the risk of all-cause morbidity and

mortality later in life (Morrison, Friedman, Wang, & Gleuck, 2008). Furthermore, the presence

of obesity and MetS during adolescence elevates the risk for several adverse clinical outcomes

including early onset of atherosclerosis, insulin resistance, type II diabetes mellitus, obstructive

sleep apnea, and psychological depression (Raj & Kumar, 2010).

A common detriment of obesity and MetS is cardiovascular autonomic nervous system

(ANS) dysfunction (Snitker, Macdonald, Ravussin, & Astrup, 2000). In healthy individuals, the

primary task of the ANS involves balancing impulses from the central nervous system to

peripheral organs via two branches, the parasympathetic nervous system (PNS) and the

sympathetic nervous system (SNS) (Freeman, Dewey, Hadley, Myers, & Froelicher, 2006). In

obese populations, disequilibrium of the ANS is reflected by reduced PNS function and/or SNS overactivity (SO). Over-activation of the SNS specifically targeting the heart, blood vessels, and kidneys appears to exacerbate the metabolic consequences associated with obesity by predisposing individuals to the development of hypertension and other cardiovascular disease (CVD) risk factors (Davy & Hall, 2004).

The relationship encompassing SNS activity, obesity, and a poor metabolic profile has been studied extensively in obese adults (Scherrer, Randlin, Tappy, Vollenweider, Jequier, & Nicod, 1994; Grassi et al., 1995; Davy & Orr, 2009). However, in obese children and adolescents, this topic has only recently received attention (Guizar, Ahuatzin, Amador, Sanchez, & Romer, 2005). As similarly observed in adults, equivocal data regarding the impact of obesity on SNS function, measured with heart rate variability (HRV), during adolescence has revealed both over- (Riva et al., 2001; Rabbia et al., 2003; Tascilar, Yokusoglu, Boyraz, Baysan, Koz, & Dundaroz, 2011) and under-activation (Vanderlei, Pastre, Junior, & Godoy, 2010). These conflicting results could be related to the difficulty in controlling several variables in this population, such as ethnicity and gender (Nagai, Matsumoto, Kita, & Moritani, 2003).

Black female adolescents have an increased risk of obesity, IR, and cardiovascular disease mortality later in life (Srinivasan, Myers, & Berenson, 2001). Current evidence suggests that normal weight black adolescents display a more effective cardiovascular ANS reactivity, marked at rest by high PNS and low SNS function, than white adolescents (Li et al., 2009; Gutin, Howe, Johnson, Humphries, Snieder, & Barbeau, 2005; Wang, Thayer, Treiber, & Snieder, 2005; Urbina, Bao, Pickoff, & Berenson, 1998). Interestingly, in a bi-racial group of healthy male and female adolescents, the detrimental effects of higher levels of adiposity on ANS function impacted black females to a greater extent, this was marked by reduced PNS activity

and elevated SNS activity. The findings of this cross-sectional study may suggest that poor body composition negatively affects cardiac ANS function to a greater extent in black female adolescents than black male or white adolescents (Gutin, Howe, Johnson, Humphries, Snieder, & Barbeau, 2005).

Adolescent cardiovascular ANS function has been explored in response to short-term evoked cardiovascular autonomic reactivity tests (Faulkner, Hathaway, & Tolley, 2003), urinary and plasma catecholamine levels (Wambach, Hossmann, Bonner, & Laaser, 1986), as well as short-term and 24-hour HRV recordings (Tanaka, Borres, Thulesius, Tamai, Ericson, & Lindblad, 2000).   A novel exercise recovery index (ERI) was recently introduced as a minimally invasive method to indirectly assess SNS control in at-risk young individuals (Yeckel, Gulanski, Zgorski, Dziura, Parish, & Sherwin, 2009). By extending the recovery period from a maximal exercise test beyond the initial rapid PNS response ($\sim$ 2 minutes), the ratio taken during the time-point into recovery where the degree of heart rate recovery normalized for oxygen consumption (HR/VO_2 plateau) initially plateaus defines the ERI value for that individual. Normalizing the HR for the prevailing VO_2 within the ERI allows for the adjustment of absolute exercise intensity and the requirement for early excess post-exercise oxygen consumption. Individuals with lower stroke volume require high HR to sustain the prevailing oxygen consumption and would thus have higher SNS activation to achieve the higher HR during recovery. This ERI was shown to provide a functional index of SNS activity.

To date, no studies have directly examined the effect of ethnicity on SNS function in obese adolescents. Therefore, the primary aim of this study is to explore the relationship between ethnicity and SNS function in obese adolescent females, assessed with the simple HR/VO_2 plat exercise recovery index (ERI). It is hypothesized that SNS activity, as measured

by the ERI, will be higher in black obese adolescent females than white obese adolescent females.

METHODS

Subjects

Obese female adolescents were recruited to participate in this study. Subjects were participants of the Virginia Commonwealth University (VCU) T.E.E.N.S. Program, a healthy weight management program administered by the Departments of Pediatrics, Health and Human Performance, and Psychology. Upon enrollment in the program, participants received a comprehensive medical, physical and psychosocial evaluation. Participants were cleared for participation in exercise testing by the T.E.E.N.S. physicians. Individuals diagnosed with any known cardiovascular or metabolic disorders (e.g., diabetes and obstructive sleep apnea (OBSA)) or taking medications that could potentially influence cardiovascular or endocrine function were excluded from the study (e.g., Thyroxine, Levothyroxine, Metformin, and Melatonin). All risks and benefits associated with the study procedures were explained and written consent/assent was obtained. This study was approved by the VCU Institutional Review Board and no costs were incurred by participants or their families. All reported measures were obtained prior to beginning the program (baseline).

Procedures

During each participant's medical visit, anthropometric measures were assessed and a resting blood sample was obtained from an antecubital vein between 8 and 10 hours after an overnight fast for assessment of total cholesterol (TC), triglycerides (TAG), low-density lipoprotein (LDL), high-density lipoprotein (HDL), glucose, and insulin. The comprehensive metabolic panel and lipid profile assays were performed in the main clinical laboratory at VCU

Health System. Subjects were scheduled within one week for a maximal exercise test and informed to report to the Human Performance Laboratory at least 4 hours postprandial.

Insulin Resistance/Sensitivity

To compute the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR), a simple mathematical approximation was employed using the product of fasting insulin and glucose values (HOMA-IR = [(fasting plasma glucose x fasting plasma insulin)/22.5]). The glucose and insulin values from the oral glucose tolerance test were performed at the Clinical Research Center (CRC) core laboratory.

Body Composition Assessment

Weight (kg) was assessed with a digital medical scale and height (cm) with a stadiometer. Body Mass Index (BMI) was then calculated (kg/m^2). Total body composition was measured with bioelectrical impedance analysis (BIA, Quantum II, RJL Systems). BIA was used to provide percent fat (%FAT) and fat-free mass (FFM).

Treadmill Graded Exercise Test

Cardiovascular fitness (CVF) was assessed using a progressive walking protocol designed to elicit maximal effort (VO_{2peak}) on a treadmill (TrackmasterTMX425C, Full Vision, Inc., Newton, KS). The treadmill protocol consisted of a 4-minute warm up at 2.5 MPH at 0% grade followed by a 2-minute stage at 3.0 MPH at 0% grade and a subsequent 2-minute stage at 3.0 MPH at 2.0% grade. Subsequent 2-minute stages were held at 3.0 MPH with the grade increasing by 3.0% each stage until volitional fatigue was attained. Heart rate (HR) was obtained at the end of every minute utilizing a heart rate monitor (Model E600, Polar electro, Kempele, Finland). Blood pressure and ratings of perceived exertion (6-20 Borg Scale) were obtained at the end of every stage. Continuous breath-by-breath measurement (Vmax Encore 29

System, VIASYS Healthcare Inc, Yorba Linda, CA) of VO_2 (L/min^{-1} & $ml/kg/min^{-1}$), and RER (VCO_2/VO_2) were obtained throughout the exercise test. Following attainment of VO_{2peak}, maximal oxygen consumption per FFM (VO_{2FFM}) was calculated by dividing absolute VO_2 (ml/min) by kilograms of FFM.

Assessment of Autonomic Function

Immediately following attainment of VO_{2peak}, subjects completed a 5-minute passive cool-down while standing as still as possible with their hands by their sides. During the 5-minute recovery period, HR was recorded every 30 seconds and VO_2 was recorded continuously. The decline in heart rate recovery at 2-minutes post-exercise (HRR-2) was used to evaluate PNS activity. To assess SNS activity, the ratio of HR (bpm) to VO_2 ($ml \cdot kg^{-1} \cdot min^{-1}$, 10 second averages) ($HR/VO_2$) was calculated for every 30-second interval and graphed against each respective time point using Microsoft Excel. The HR/VO_2 value representing the time point during recovery where the ratio initially reached a plateau was termed ERI and taken as a functional index of sympathetic activity (Yeckel, Gulanski, Zgorski, Dziura, Parish, & Sherwin, 2009).

Statistical Analyses

A one-way ANOVA (SPSS, Chicago, IL: V19.0) was used to compare subject demographics between the two groups. Simple associations between ERI and health characteristics were evaluated using Pearson product-moment correlations. Multiple linear regression was performed to assess the independent variability of ERI with %FAT, HOMA-IR, fasting insulin, fasting TAG, VO_{2FFM}, and SBP. Log transformations of the insulin sensitivity indices were used to satisfy assumptions of the statistical methods. All data are expressed as mean ± SD unless otherwise noted.

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RESULTS

Sixty-one adolescents participated in the study (Black: N= 49; White: N= 12). Subject characteristics for both black and white females are presented in Table 1. Resting insulin concentrations were unable to be determined in two of the black females. Therefore, the black obese female group had 47 subjects for all fasting insulin and HOMA-IR data analyses. There were no significant differences with regard to age or BMI between the two groups ($P = 0.506$ and $P = 0.119$, respectively). Black females had significantly higher ERI values than white females (29.8 ± 6.4 vs. 24.1 ± 3.1; $P = 0.004$) as displayed in Figure 1. Additionally, the black females displayed significantly higher SBP values ($P = 0.012$) and lower fasting TAG concentrations ($P = 0.001$) than the white females.

Pearson product-moment correlations between ERI and health variables in both black and white females are presented in Table 2. A significant relationship between ERI and VO_{2FFM} was present in only the obese black females (Figure 2). Percent fat approached, but failed to reach significance with ERI ($r = 0.275$, $P = 0.056$). No significant relationships were observed in the white females between ERI and the health variables ($P \geq 0.374$).

A multiple linear regression analysis was performed to determine relative contributions of various health characteristics to ERI, as displayed in Table 3. The dependent variable tested for each group was ERI. The independent variables tested were %FAT, HOMA-IR, fasting insulin, fasting TAG, VO_{2FFM}, and SBP. In the black females, 27.0% ($P = 0.037$) of the ERI variance was explained for by the independent variables with significant contributions from %FAT (10.0%) and VO_{2FFM} (9.6%). White females had 37.5% (P = 0.788) of the variance explained, however none of the independent variables provided a significant contribution.

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Additionally, semi-partial correlations, presented in Table 3, describe the unique contribution to explaining the dependent variable when variance was controlled.

DISCUSSION

To our knowledge, this is the first study to examine the effects of ethnicity on SNS function in obese adolescent females. The major finding of this study was that black obese adolescent females display higher SNS activity than their white counterparts as indexed by the ERI. Overactivation of the SNS is a common hallmark of the obese state and thus has been implicated as a link between excess adiposity and cardiovascular disease risk (Raj, 2012), especially in black individuals (Eslami & Tuck, 2003). As suggested in the current study, pathophysiological mechanisms related to poor cardiovascular outcomes in adults are already operative in obese adolescents. In the United States, adolescent obesity is more common in black individuals than in white, particularly black females (Liu et al., 1993; Ogden, Carrol, Curtin, Lamb, & Flegal, 2010). Various studies have shown ethnic differences in ANS function in adult (Abate et al., 2001; Abbas et al., 2010; Weyer, Pratley, Snitker, Spraul, Ravussin, & Tatarami, 2000; Choi et al., 2006) and healthy youth (Wang, Thayer, Treiber, & Sneider, 2005; Guitin, 2005) populations. However, little is known in regards to ANS function and ethnic differences in obese adolescents.

Much of the evidence evaluating ethnic differences in ANS function in healthy adolescents indicates that black individuals display more favorable resting HRV profiles than white individuals (Liao, Barnes, Chambless, Simpson, Sorlie, & Heiss, 1995; Urbina, Bao, Pickoff, & Berenson, 1998; Wang, Thayer, Treiber, & Snieder, 2005). Studies exploring gender differences in resting HRV have revealed equivocal results (Evans et al., 2001; Koskinen et al., 2009; Umetani, Singer, McCraty, Atkinson, 1998; Bomemeier et al., 2003). Few studies have

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directly evaluated the effects of ethnicity on ANS function in females. In line with the present findings, Gonzalez-Trapega et al. (2000) uncovered ethnic differences in SNS activity in a diverse sample of black and white, male and female adults. Basal plasma epinephrine (E) levels were measured to assess SNS function. No differences in plasma E levels were found between white males or black males and black females. However, plasma E levels were significantly higher in black females than in white, suggesting that black females display elevated SNS activity at rest when compared to white females. The results within the current study support the ERI as a potential tool in assessing SO and the disproportionately high risk of obesity, IR, and CVD mortality later in life of black adolescent females (Srinivasan, Myers, & Berenson, 2001).

The cross-sectional data of the current study revealed a significant inverse relationship between ERI and VO_{2FFM} in the black females only. Gutin et al. (2005) revealed similar findings associated with impaired ANS function in their bi-racial group of 304 non-obese male and female adolescents. Subjects completed a graded treadmill test to exhaustion for the assessment of CVF and ANS balance was calculated from HRV. With gender combined, the black adolescents expressed more favorable HRV profiles, marked by higher PNS activity, than the white adolescents. Higher CVF was significantly associated with more favorable PNS function in black females but was not significantly related to PNS activity in males or white females. Interestingly, when the effects of body composition on ANS function were analyzed, reduced PNS activity coupled with an increase in SNS activity was revealed. These deleterious effects of increasing adiposity on ANS control were only significant in the black adolescents, particularly females. Supporting the present implications in obese adolescents, these findings may suggest that as weight gain ensues and CVF deteriorates, cardiac ANS function is compromised to a

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greater extent in black female adolescents than black male or white adolescents (Gutin, Howe,

Johnson, Humphries, Snieder, & Barbeau, 2005).

Autonomic function in adolescence has been shown to be mediated by several metabolic

factors including body composition (Li et al., 2009), IR (Tascilar, Yokusoglu, Boyraz, Baysan,

Koz, & Dundaroz, 2011), leptin (Kaufman, Kaiser, Steinberger, Kelly, & Dengel, 2007), SBP

(Guizar, Ahuatzin, Amador, Sanchez, & Romer, 2005) and CVF (Gutin, Howe, Johnson,

Humphries, Snieder, & Barbeau, 2005). Given the previous evidence describing these

relationships, we used multiple regression to adjust for potential covariates of ERI including

%FAT, HOMA-IR, fasting insulin, fasting TAG, VO_{2FFM}, and SBP. The results of the present

study suggest that only %FAT and VO_{2FFM} were able to explain a significant independent portion

of the ERI in the black females. The implications of our findings agree with a previous study

performed in a bi-racial adult population. Abate et al., (2001) used microneurographic

recordings to explore relationships between adiposity and SNS function in normotensive black

and white adults of similar age and BMI. Sympathetic nervous system activity in black females

was closely correlated to BMI. Contrary to the present study, this relationship was also observed

in their group of white females. In an obese population regional SNS modulation varies in

magnitude to various organ systems (Davy & Orr, 2009). Therefore, the different techniques

used to assess SNS function between our study and Abate et al. could explain the lack of

agreement in findings for the white females.

As previously described, the relationship between MetS, obesity, and SNS overactivation

is affected by an array of factors deeming this association complex. Several hypotheses have

been proposed to explain the over-expression of SNS activity observed in obesity (Straznicky,

Eikelis, Lambert, & Esler, 2008). These include (1) leptin concentration, which in obese

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adolescents has been shown to explain a significant portion of the variance in SO (Guizar, Ahuatzin, Amador, Sanchez, & Romer, 2005); (2) IR, which has been shown to cause higher SNS activity in obese adolescents when compared to non-IR obese controls (Tascilar, Yokusoglu, Boyraz, Baysan, Koz, & Dundaroz, 2011); and (3) OBSA, which has been shown to result in higher SNS activity in obese adolescents when compared to obese controls without OBSA (Snow, Khalyfa, Serpero, Capdevila, Kim, Buazzo, & Gozal, 2009). Due to the cross-sectional nature of the current study, we were only able to make observations regarding relationships between possible causative mechanisms for the SO observed in our obese black females. Leptin was not measured in this study and subjects with OBSA were excluded from the analysis. As a measure of IR, HOMA-IR was not related to ERI in either group. This is in disagreement with a previous finding that suggested HOMA-IR was associated with ANS dysfunction, as defined by exercise recovery kinetics, in a group of young individuals with a wide range of ERI values (9 to 34) (Yeckel et. al., 2009). It is important to note that in the current study, the black females had a significantly higher ERI than their white counterparts. However, both groups had higher ERI values than previously reported in a non-obese population, thus potentially limiting the ability of HOMA-IR to assess relationships without a larger variance in ERI.

The results within the current study should be taken in consideration of the following limitations. The results of this study support differences in SNS activity between black and white obese female adolescents. However, this finding is supported by a tool that has only been validated using an indirect method for assessing SNS function, high-carbohydrate meal-induced thermogenesis. Additionally, this study lacks a normal weight control group to further compare ethnic differences. Lastly, we did not control for menstrual cycle (McKinley et al., 2009) or

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tanner stage (Tanaka, Borres, Thulesius, Tamai, Ericson, Lindblad, 2000) both of which have been shown to impact ANS function.

In summary, the findings within the scope of the current study demonstrate that black obese adolescent females may display higher SNS activity when compared to their white counterparts. It has been postulated that elevated SNS activity in adolescence plays a pivotal role in the development of hypertension, CVD, and type II diabetes later in life (Srinivasan, Myers, & Berenson, 2001), therefore based on the findings of the current study, black obese female adolescents may be at a higher risk for the development of disease later in life. Additionally, %FAT and VO_{2FFM} were significant independent predictors of the variance in SNS activity in the black females. Thus, physical training aimed at improving VO_{2max} coupled with appropriate dieting may elicit the most favorable changes in ANS function in black adolescent obese females.

Table 1   Subject characteristics.

Variable	Black	White
Age (years)	13.7 ± 1.7	13.3 ± 2.1
BMI (kg/m^2)	38.2 ± 6.2	35.1 ± 5.4
Percent Fat (%FAT)	52.1 ± 4.6	49.9 ± 5.1
Fitness (VO$_{2Peak}$ [L/min])	2.4 ± 0.4	2.4 ± 0.3
Fitness (VO$_{2FFM}$ [mL/kg(FFM)/min])	50.0 ± 7.4	54.0 ± 6.4
Fasting Insulin (μU/mL)	19.1 ± 15.4	16.1 ± 10.9
HOMA-IR	4.0 ± 3.4	3.4 ± 2.4
Fasting TAG (mg/dL)	75.8 ± 28.0*	114.5 ± 56.0
Total Cholesterol (mg/dL)	155.8 ± 36.7	158.2 ± 30.0
LDL Cholesterol (mg/dL)	79.72 ± 36.0	92.13 ± 20.3
HDL Cholesterol (mg/dL)	43.1 ± 12.4	41.67 ± 8.8
Systolic Blood Pressure (mmHg)	119.2 ± 9.7*	111.0 ± 9.3
Diastolic Blood Pressure (mmHg)	64.6 ± 5.4	61.9 ± 6.7
ERI	29.8 ± 6.4*	24.1 ± 3.1

* $P < 0.05$, Black vs. White. Values are mean $\pm$ SD. BMI, Body Mass Index; VO$_{2peak}$, Maximal Oxygen Consumption; VO$_{2FFM}$, Maximal Oxygen Consumption per kg Fat-Free Mass; HOMA-IR, Homeostasis Model Assessment for Insulin Resistance; TAG, Triglycerides; LDL, Low Density Lipoprotein; HDL, High Density Lipoprotein; ERI, Exercise Recovery Index.

Table 2   Pearson Product-Moment Correlations to ERI

| Variable	Black	White
Percent Fat (%FAT)	0.275	0.095
logHOMA-IR	0.162	0.215
Fasting Insulin (μU/mL)	0.102	0.094
Fasting TAG (mg/dL)	0.154	0.282
Systolic Blood Pressure (mmHg)	-0.138	0.204
Fitness (VO$_{2FFM}$ [mL/kg(FFM)/min])	-0.347*	0.026

* $P < 0.05$, Values are Correlation Coefficients (r). ERI, Exercise Recovery Index; HOMA-IR, Homeostasis Model Assessment for Insulin Resistance; TAG, Triglycerides; VO$_{2FFM}$, Maximal Oxygen Consumption per kg Fat-Free Mass

Table 3   Multiple Linear-Regression for ERI as the Dependent Variable

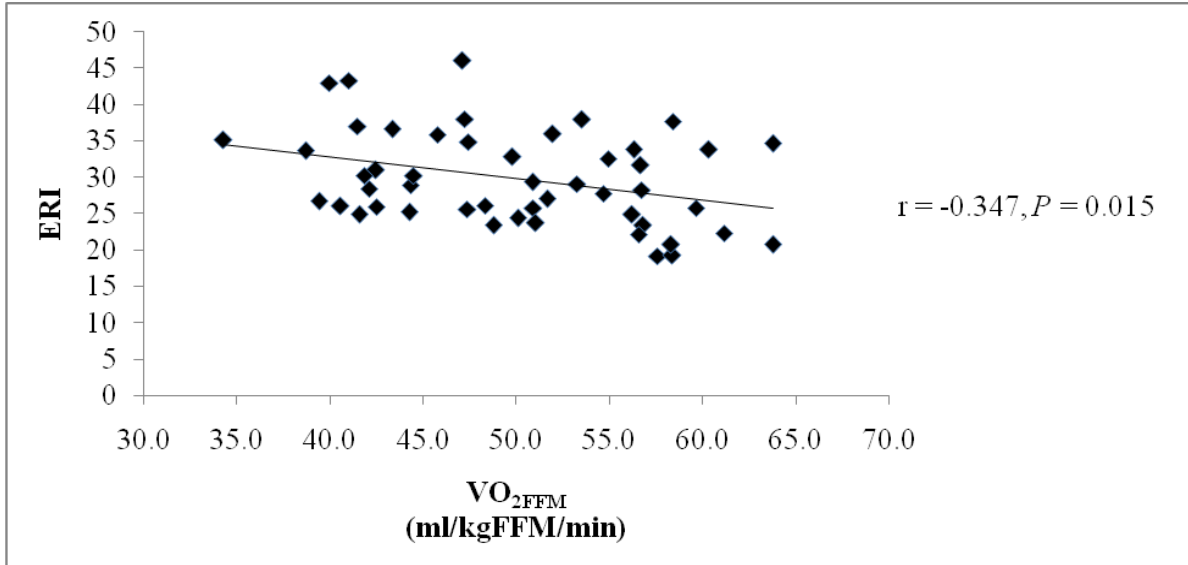| Variable Coefficient (β)	Standardized	Semi-Partial (r)
Black ($R^2 = 0.273$, $P = 0.037$)		
Percent Fat (%FAT)*	0.360	0.326
logHOMA-IR	0.291	0.159
Fasting Insulin (μU/mL)	-0.134	-0.075
Fasting TAG (mg/dL)	0.001	0.001
Systolic Blood Pressure (mmHg)	-0.23	-0.214
Fitness (VO$_{2FFM}$ [mL/kg(FFM)/min])*	-0.313	-0.310
White ($R^2 = 0.375$, $P = 0.788$)		
Percent Fat (%FAT)	-0.284	-0.152
logHOMA-IR	1.317	0.353
Fasting Insulin (μU/mL)	-1.069	-0.278
Fasting TAG (mg/dL)	0.574	0.364
Systolic Blood Pressure (mmHg)	0.298	0.204
Fitness (VO$_{2FFM}$ [mL/kg(FFM)/min])	-0.175	-0.117

* $P < 0.05$: ERI, Exercise Recovery Index; HOMA-IR, Homeostasis Model Assessment for Insulin Resistance; TAG, Triglycerides; VO$_{2FFM}$, Maximal Oxygen Consumption per kg Fat-Free Mass

Figure 1 Exercise Recovery Data between Groups
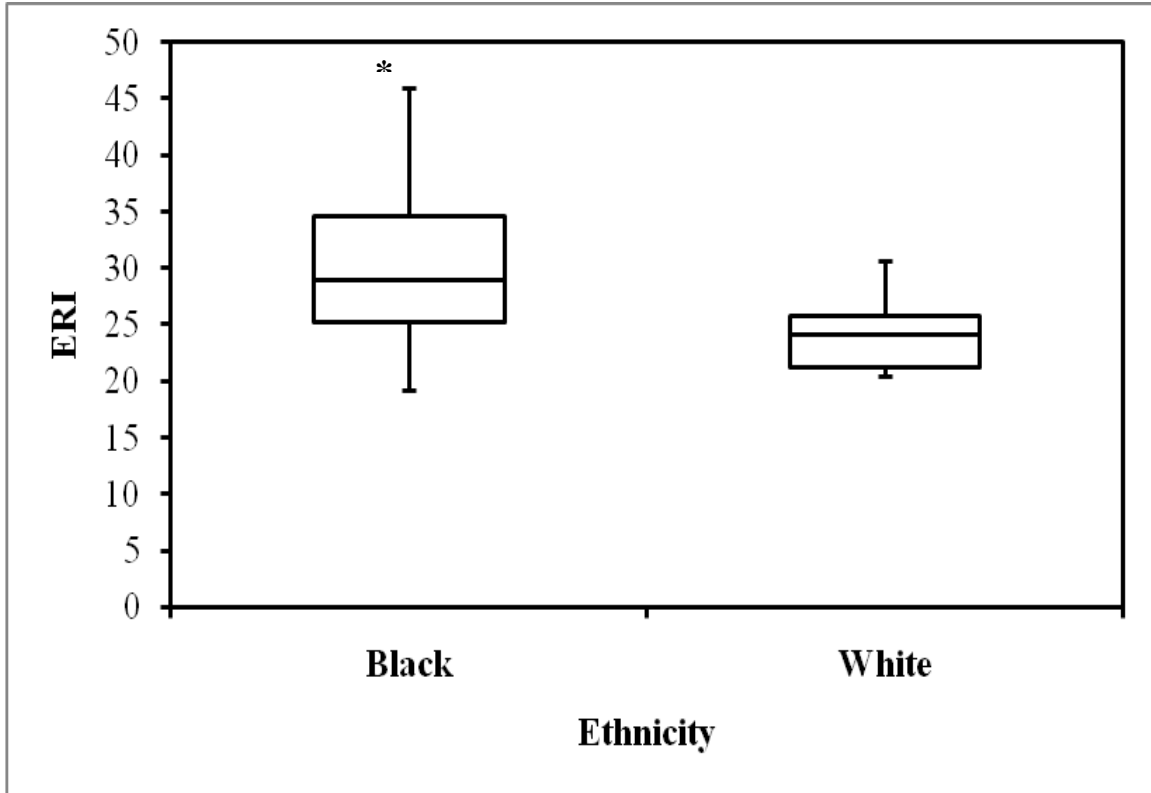
* *P* = 0.004; Box plot line is median value, box is divided as upper and lower quartiles.

Figure 2   Relationship between ERI and VO$_{2FFM}$ in Black Adolescent Females

The scatter plot shows ERI on the y-axis (0 to 50) versus VO$_{2FFM}$ (ml/kgFFM/min) on the x-axis (30.0 to 70.0). The annotation reads: $r = -0.347, P = 0.015$

List of References

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Vita

Stacey Lewis Hall was born on May 22, 1987, in Mathews County, Virginia and is an American citizen. She graduated from Mathews High School, Mathews, Virginia in 2005. She received her Bachelor of Science in Health, Physical, Education, and Exercise Science from Virginia Commonwealth University, Richmond, Virginia in 2009. She was granted a research assistantship with the Human Movement Sciences graduate program in the Department of Health and Human Performance at Virginia Commonwealth University, Richmond, Virginia in 2009.