METABOLIC SYNDROME, INFLAMMATION, HEART RATE VARIABILITY, AND FITNESS IN OBESE AFRICAN AMERICAN YOUTH

A Dissertation
Presented for
The Graduate Studies Council
The University of Tennessee
Health Science Center

In Partial Fulfillment
Of the Requirements for the Degree
Doctor of Philosophy
From the University of Tennessee

By
Belinda J. Fleming
May 2009
DEDICATION

This work is dedicated to the memory of my dad, Bobby Costley (1932-2007), who instilled in me the lessons of hard work and persistence; the memory of my brother, Daryl Dougharty (1963-2008), who taught me the benefits of forgiveness and laughter; and to the memory of Jasper and Cosmo (1990-2007), who always showed me loyalty, devotion, and love. I miss them all.
ACKNOWLEDGEMENTS

Obviously a dissertation is not possible without the personal and practical support of numerous people. Thus my sincere gratitude goes to many for their love, support, and patience over the last few years.

My deepest gratitude is to my advisor, Dr. Patricia Cowan. I have been fortunate to have an advisor who gave me the freedom to explore my own observations and ideas, and at the same time provided me the advice and support to recover when my steps faltered. Patty taught me how to question thoughts and express ideas. Her patience and support helped me overcome many crisis situations and finish this dissertation.

My advisor and friend, Dr. Margaret Hartig, has been always there to listen and give advice. I am deeply grateful to her for the long discussions that helped me sort out the details of my work. I am also thankful to her for encouraging the use of correct grammar and consistent notation in my writings and for carefully reading and commenting on countless revisions of this manuscript.

Dr. Donna Hathaway’s insightful comments and constructive criticisms at different stages of my research were stimulating and helped me focus my thoughts and the direction of this paper. I am grateful to her for holding me to high research standards.

Dr. Phyllis Richey sets high standards for students and encourages and guides them to meet those standards. I am indebted to her for her continuous encouragement and guidance.

I am grateful to Dr. Zoila Sanchez for her encouragement and practical advice. I am also thankful to her for reading my chapters; commenting on my views and stepping in—thus helping me reach my goals.

This dissertation would not have been possible without the expert guidance of, Dr Pedro Velasquez-Mieyer. He trusted me with his previous work and he was always readily available. He responded to my ideas more quickly than I could have hoped and his comments were always extremely perceptive, helpful, and appropriate. He listened to my ideas as if I were already a peer.

Many people on the faculty and staff of the College of Nursing assisted and encouraged me in various ways during my course of studies. I am especially grateful to Dr Patricia Cunningham, Dr Patricia Speck, Dr. Ann Cashion, Dr. Mona Wicks, Dr. Veronica Engle, and Dr. Carol Thompson for all that they have taught me.

I am also grateful to the following former or current doctoral students at University of Tennessee Health Science Center, for their various forms of support during my graduate study, especially Shirleatha Lee, Queen Henry-Okafor, Carol Warren-
Many friends have helped me stay sane through these difficult years. Their support and care helped me overcome setbacks and stay focused on my graduate study. I greatly value their friendship and I deeply appreciate their belief in me. I want to especially thank Andi Harrison, Marcia Hall, Nancy Mc Cann, Julie Smith, Jan Harrell, the staff at May Medical Group, and the staff at the Military Acute Care Department, Sewells Branch Medical Clinic, Naval Support Activity Norfolk, Virginia.

Finally, and most importantly, none of this would have been possible without the love and patience of my family. My immediate family has been a constant source of love, concern, support and strength all these years. I would like to thank my husband, Gary. His support, encouragement, quiet patience and unwavering love were undeniably the foundation upon which the past thirty plus years of my life have been built. His tolerance of my occasional rude, offensive and wretched moods is a testament in itself of his unyielding loyalty and love. I would like to express my heart-felt gratitude to my children, Sarah and Sam, for their faith in me. I hope I have shown them dreams come true with hard work and that one is never too old to learn and grow. My extended family has also aided and encouraged me throughout this endeavor. I have to give a special mention for the support given by Christopher Reyes and Vernie Kuglin. I warmly appreciate their generosity and understanding.
ABSTRACT

**Purpose.** The purposes of this dissertation were to (1) explore the relationships among fitness, heart rate variability (HRV), inflammation and components of the Metabolic Syndrome in obese African American youth participating in a supervised weight management program, (2) examine the effect of change in severity of obesity on these variables, and (3) identify predictors of weight loss.

**Method.** This study consisted of a post-hoc analysis of existing pre and post-intervention data obtained from 50 African-American youth (70% female, aged 7-18 years). Anthropometric assessment of height, weight, waist circumference, systolic blood pressure, body mass index, body mass index percentile ranges, and relative body mass index were conducted. Laboratory measures included high-density lipoprotein cholesterol, triglycerides, fibrinogen, and C-reactive protein levels, and fasting and 2-hr postprandial insulin and glucose levels obtained during a mixed meal tolerance test for determination of impaired glucose tolerance and insulin resistance. Aerobic fitness was assessed by cardiopulmonary maximal treadmill exercise using the Branching Protocol (VO2max). Heart rate variability was measured with a 24-hour Holter monitor and measures of circadian fluctuation (SDNN), parasympathetic function (HF), and sympathetic/parasympathetic balance (LF/HF ratio) were calculated. Measures were repeated at 6 months. Data were analyzed using descriptive statistics, Pearson’s correlation coefficient, non-parametric t-tests and multiple linear regression. Metabolic Syndrome was defined based on World Health Organization definition with age, gender, and race-specific cut-points.

**Results.** Baseline measures revealed the following means: age 12.9 ± 2.9, weight 92.2 kg ± 28.4, relative body mass index 195.5 ± 42.4, HF 5.9 [ln(ms²)] ± 0.9, SDNN 128.1(ms) ± 38.2, LF/HF ratio 1.1 ± 0.1, VO2max 18.8 ± 4.5 mg/kg/min, C-reactive protein 0.75 mg/L ± 1.34, fibrinogen 372.64 mg/dl ± 71.12. The prevalence of the Metabolic Syndrome was 46% based on 39 subjects with complete data sets. The presence of the individual Metabolic Syndrome components, for the entire sample, was as follows: systolic blood pressure 44%, high density lipoprotein 20%, triglycerides 40%, impaired glucose tolerance 18%, insulin resistance 82%, and waist circumference 73%. Inflammation was common (elevated C-reactive protein 45%, elevated fibrinogen 42%). VO2max was positively correlated with HF (r = 0.41, p = 0.004) and SDNN (r = 0.39, p = 0.007) and negatively with fibrinogen (r = -0.53, p = 0.0002) and relative body mass index (r = -0.47, p = 0.0007). Relative body mass index was positively associated with C-reactive protein (r = 0.38, p = 0.01) and fibrinogen (r = 0.51, p = 0.003). Those with impaired glucose tolerance did not differ in HRV measures, fitness, or inflammation. Insulin resistance was associated with HF (p = 0.004) and fibrinogen (p = 0.02). Waist circumference was associated with LF/HF ratio (p = 0.02). Lower high density lipoprotein was associated with higher fibrinogen (p = 0.05). There were no significant differences in HRV, VO2max, or inflammation in youth with or without Metabolic Syndrome. Change in relative body mass index was associated with improved SDNN (r = 0.36, p = 0.04), and there was a trend toward better VO2max (r = -0.30, p = 0.07) and HF (r
Male gender and higher baseline fitness accounted for 28% of the variance in RBMI change.

**Conclusions.** Metabolic Syndrome is common in obese youth, even in younger children. Insulin resistance, even in the absence of the Metabolic Syndrome, negatively affects HRV. Mild weight loss is associated with improvements in SDNN, a risk factor for sudden death. Strategies to improve weight loss and fitness in severely obese African American youth are needed.
# TABLE OF CONTENTS

## CHAPTER 1: INTRODUCTION ................................................................................................. 1
- Overview .......................................................................................................................... 1
- Purpose ......................................................................................................................... 2
- Significance .................................................................................................................. 3
- Conceptual Framework ............................................................................................... 4
- Major Concepts and Definitions .................................................................................. 7
  - Obesity ....................................................................................................................... 7
  - Obesity Severity ....................................................................................................... 8
  - Weight Loss .............................................................................................................. 8
  - Metabolic Syndrome ............................................................................................... 8
  - Inflammation .......................................................................................................... 11
  - Heart Rate Variability ........................................................................................... 11
  - Fitness ....................................................................................................................... 11
- Assumptions ................................................................................................................ 12
- Limitations .................................................................................................................. 12

## CHAPTER 2: REVIEW OF LITERATURE ......................................................................... 13
- Introduction .................................................................................................................. 13
- Metabolic Syndrome .................................................................................................... 13
- Metabolic Syndrome and Youth .................................................................................. 15
  - Normative Values for the Components of the Metabolic Syndrome in Youth ....... 17
  - Prevalence of the Metabolic Syndrome .................................................................. 24
  - Conclusion ............................................................................................................. 26
- Heart Rate Variability ................................................................................................. 26
  - Autonomic Nervous System .................................................................................... 26
  - Measuring HRV ....................................................................................................... 27
  - Time Domain .......................................................................................................... 27
  - Frequency Domain ................................................................................................. 28
- HRV in Children ........................................................................................................... 28
  - Diabetes, Insulin Resistance, and HRV in Children ............................................... 28
  - Obesity and HRV in Children ................................................................................. 29
  - Hypertension and HRV in Children ........................................................................ 29
  - Age and HRV in Children ..................................................................................... 30
  - Gender and HRV in Children ................................................................................. 30
  - Ethnicity and HRV in Children .............................................................................. 31
  - Physical Activity and HRV in Children .................................................................. 32
- Effective Programs for Weight Management ............................................................... 32
  - Diet Component ....................................................................................................... 33
  - Physical Activity Component .................................................................................. 34
  - Conclusion .............................................................................................................. 35
- Effect of Weight Loss on Fitness, HRV, and the Components of the Metabolic Syndrome .................................................................................................................. 36
- Conclusion .................................................................................................................. 37
## LIST OF TABLES

Table 1.1  Metabolic Syndrome Criteria ...................................................................... 10
Table 3.1  Categories of Glucose Metabolism ............................................................ 44
Table 4.1  Characteristics of the Sample Population at Baseline .............................. 50
Table 4.2  Presence of Metabolic Syndrome Components in Total Population ....... 52
Table 4.3  Baseline HRV, Fitness, and Inflammation Markers in Total Sample ........ 52
Table 4.4  Correlation Coefficients among HRV Measures, Fitness, Inflammation Markers, and Severity of Obesity in the Total Sample ........................................ 54
Table 4.5  Differences in HRV, Fitness, and Inflammation Markers Based on Presence of Impaired Glucose Tolerance (IGT) ................................................................. 55
Table 4.6  Differences in HRV, Fitness, and Inflammation Based on Insulin Resistance .......................................................................................................................... 56
Table 4.7  Differences in HRV, Fitness, and Inflammation Based on Metabolic Syndrome Component of Central Adiposity .............................................................. 57
Table 4.8  Differences in HRV, Fitness, and Inflammation Based on Metabolic Syndrome Component of HDL-cholesterol .............................................................. 58
Table 4.9  Differences in HRV, Fitness, and Inflammation Based on Metabolic Syndrome Component of Elevated Systolic Blood Pressure ...................................... 59
Table 4.10 Differences in HRV, Fitness and Inflammation Based on Metabolic Syndrome Component of Triglycerides ................................................................. 60
Table 4.11 Differences in HRV, Fitness and Inflammation Based on the Presence of the Metabolic Syndrome Using QUICKI as the Measure of Insulin Resistance ................................................................. 61
Table 4.12 Differences in HRV, Fitness and Inflammation Based on the Presence of the Metabolic Syndrome Using Acanthosis Nigricans as the Measure of Insulin Resistance ................................................................. 62
Table 4.13 Characteristics of the Sub-sample at the 6 Month Time Point .............. 63
Table 4.14 Correlation of Changes of RBMI, Fitness (VO_{2\text{max}}), and HRV ........... 64
**LIST OF ABBREVIATIONS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AACE</td>
<td>American Association of Clinical Endocrinologists</td>
</tr>
<tr>
<td>ADA</td>
<td>American Diabetes Association</td>
</tr>
<tr>
<td>AHA</td>
<td>American Heart Association</td>
</tr>
<tr>
<td>ARIC</td>
<td>atherosclerosis risks in communities</td>
</tr>
<tr>
<td>ATP</td>
<td>Adult Treatment Panel</td>
</tr>
<tr>
<td>BMI</td>
<td>body mass index</td>
</tr>
<tr>
<td>BP</td>
<td>blood pressure</td>
</tr>
<tr>
<td>b/min</td>
<td>beats per minute</td>
</tr>
<tr>
<td>CDC</td>
<td>Centers for Disease Control</td>
</tr>
<tr>
<td>CHD</td>
<td>chronic heart disease</td>
</tr>
<tr>
<td>CRP</td>
<td>C-reactive protein</td>
</tr>
<tr>
<td>CVA</td>
<td>cerebral vascular accident</td>
</tr>
<tr>
<td>CVD</td>
<td>cardiovascular disease</td>
</tr>
<tr>
<td>CVF</td>
<td>cardiovascular fitness</td>
</tr>
<tr>
<td>DBP</td>
<td>diastolic blood pressure</td>
</tr>
<tr>
<td>DEXA</td>
<td>dual energy X-ray absorptiometry</td>
</tr>
<tr>
<td>EGIR</td>
<td>European Group for the Study of Insulin Resistance</td>
</tr>
<tr>
<td>EKG</td>
<td>electrocardiogram</td>
</tr>
<tr>
<td>FMD</td>
<td>brachial artery flow-mediated dilation</td>
</tr>
<tr>
<td>GT</td>
<td>glucose tolerance</td>
</tr>
<tr>
<td>HDL</td>
<td>high density lipoprotein</td>
</tr>
<tr>
<td>HELP Center</td>
<td>Center for Health Evaluation and Lifestyle Promotion</td>
</tr>
<tr>
<td>HF</td>
<td>high frequency</td>
</tr>
<tr>
<td>HOMA</td>
<td>homeostasis model assessment</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>homeostasis model assessment, insulin resistance</td>
</tr>
<tr>
<td>HRV</td>
<td>heart rate variability</td>
</tr>
<tr>
<td>HTN</td>
<td>hypertension</td>
</tr>
<tr>
<td>IDF</td>
<td>International Diabetes Federation</td>
</tr>
<tr>
<td>IGM</td>
<td>impaired glucose metabolism</td>
</tr>
<tr>
<td>IGT</td>
<td>impaired glucose tolerance</td>
</tr>
<tr>
<td>IR</td>
<td>insulin resistance</td>
</tr>
<tr>
<td>IRS</td>
<td>Insulin Resistance Syndrome</td>
</tr>
<tr>
<td>LF</td>
<td>low frequency</td>
</tr>
<tr>
<td>M</td>
<td>metabolic equivalent</td>
</tr>
<tr>
<td>MMTT</td>
<td>mixed meal tolerance test</td>
</tr>
<tr>
<td>NCEP</td>
<td>National Cholesterol Education Program</td>
</tr>
<tr>
<td>NCHS</td>
<td>National Center of Health Statistics</td>
</tr>
<tr>
<td>NHANES</td>
<td>National Health and Nutrition Examination Survey</td>
</tr>
<tr>
<td>NICHD</td>
<td>National Institute of Child Health and Human Development</td>
</tr>
<tr>
<td>NIDDKD</td>
<td>National Institute of Diabetes and Digestive and Kidney Diseases</td>
</tr>
<tr>
<td>NHLBI</td>
<td>National Heart, Lung, and Blood Institute</td>
</tr>
<tr>
<td>NIH</td>
<td>National Institutes of Health</td>
</tr>
<tr>
<td>NIHORD</td>
<td>National Institutes of Health Office of Rare Diseases (part of NIH)</td>
</tr>
<tr>
<td>Acronym</td>
<td>Description</td>
</tr>
<tr>
<td>---------</td>
<td>-------------</td>
</tr>
<tr>
<td>OGTT</td>
<td>oral glucose tolerance test</td>
</tr>
<tr>
<td>OR</td>
<td>odds ratio</td>
</tr>
<tr>
<td>PA</td>
<td>physical activity</td>
</tr>
<tr>
<td>PMSWG</td>
<td>Pediatric Metabolic Syndrome Working Group</td>
</tr>
<tr>
<td>PSD</td>
<td>power spectral density</td>
</tr>
<tr>
<td>QUICKI</td>
<td>quantitative insulin-sensitivity check index</td>
</tr>
<tr>
<td>RBMI</td>
<td>relative body mass index</td>
</tr>
<tr>
<td>RSA</td>
<td>respiratory sinus arrhythmia</td>
</tr>
<tr>
<td>SBP</td>
<td>systolic blood pressure</td>
</tr>
<tr>
<td>SD</td>
<td>standard deviation</td>
</tr>
<tr>
<td>SDNN</td>
<td>standard deviation of R-R intervals of QRS complexes of normal beats</td>
</tr>
<tr>
<td>T2DM</td>
<td>type 2 diabetes mellitus</td>
</tr>
<tr>
<td>TG</td>
<td>triglyceride</td>
</tr>
<tr>
<td>ULF</td>
<td>ultra low frequency</td>
</tr>
<tr>
<td>VLF</td>
<td>very low frequency</td>
</tr>
<tr>
<td>VO2max</td>
<td>oxygen consumption at maximal exercise</td>
</tr>
<tr>
<td>VO2peak</td>
<td>peak oxygen uptake</td>
</tr>
<tr>
<td>WC</td>
<td>waist circumference</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>WHR</td>
<td>waist-hip ratio</td>
</tr>
</tbody>
</table>
CHAPTER 1: INTRODUCTION

Overview

Childhood obesity has increased in epidemic fashion in the United States with African American youth being almost twice as likely as Caucasians to be obese (Ogden, Flegal, Carroll, & Johnson, 2002). The growing problem of obesity in America’s children has led policymakers to rank it as a critical public health threat. In fact, the World Health Organization calls obesity an obvious but overlooked public health problem (Rigby, Kumanyika, & James, 2004). Obesity is a risk factor for a variety of chronic diseases, including cardiovascular disease (CVD), stroke, type 2 diabetes mellitus (T2DM), gout, thrombosis, hypertension and infertility. It is evident that what was once known as adult disease is established in childhood; as manifested by the increased incidence of concomitant dyslipidemia, hypertension, and impaired glucose metabolism seen in overweight youth.

The Metabolic Syndrome is characterized by a clustering of risk factors, which includes obesity, hypertension, dyslipidemia, glucose intolerance and insulin resistance (IR). Originally described in 1988 by Reaven, the Metabolic Syndrome (also known as Syndrome X or the Insulin Resistance Syndrome) has subsequently been identified as a precursor to both CVD and T2DM (Lorenzo, Serrano-Rios et al., 2007; Morrison, Friedman, Wang, & Glueck, 2008). Whether the clustering of these risk factors reflects interrelations among the risk variables or is a manifestation of a dominant underlying common factor has not been established and has not been extensively studied in youth.

Inflammatory markers and heart rate variability (HRV) may provide measures of additional risk for CVD and T2DM in obese youth. Risk factors for CVD and T2DM extend beyond the current Metabolic Syndrome criteria. Sub-clinical inflammation, not just obesity and IR, is hypothesized to be among underlying mechanisms for the clustering of risk factors found in Metabolic Syndrome. Inflammation has been proposed as a common pathway for CVD and T2DM (Schmidt et al., 1999).

Additionally, Perciaccante, Fiorentini, Paris, Serra, and Tubani (2006) suggested that IR, one component of the Metabolic Syndrome, causes autonomic dysfunction. Impaired HRV, one measure of cardiac autonomic function, has been identified as a risk factor for sudden cardiac death in adults and youth. Several studies support the linkage between obesity and diminished parasympathetic measures of HRV in youth (Gutin, Howe et al., 2005); while increased duration of obesity was associated with poorer HRV measurements sympathetic:parasympathetic balance (Rabbia et al., 2003).

Large cohort studies support the benefit of physical activity and fitness in attenuating the risk of CVD (Hu et al., 2000) and T2DM (Knowler et al., 2002), and all-cause mortality in overweight and obese adults (Blair & Brodney, 1999; Farrell, Braun, Barlow, Cheng, & Blair, 2002; Lee, Blair, & Jackson, 1999; Wei et al., 1999). Poor
fitness and physical inactivity also are associated with a substantially increased risk of the Metabolic Syndrome (Laaksonen et al., 2002).

However, in youth the relationship of fitness to various Metabolic Syndrome components has yielded equivocal results (Katzmarzyk, Malina, & Bouchard, 1999; McMurray et al., 2002). Recent fitness trials suggest that exercise programs improve some Metabolic Syndrome measures (Kelley & Kelley, 2007; Meyer, Kundt, Lenschow, Schuff-Werner, & Kienast, 2006) and inflammatory markers (Meyer et al., 2006) in overweight youth and therefore may reverse early development of atherosclerosis in youth. Youth with Metabolic Syndrome exhibit higher levels of inflammation than those without the Metabolic Syndrome. Thus, inflammation in obese youth may pose an additive risk for CVD and T2DM beyond that incurred by the Metabolic Syndrome.

The goals of weight management programs in youth include weight reduction or stabilization of weight and reduction in markers of health risk. These programs typically incorporate lifestyle modifications in diet and exercise with education and behavioral strategies. Weight management programs that target both the child and parents appear to be more efficacious than those focused on the child alone (Brownell & Wadden, 1984; Saelens et al., 2002). A limited number of studies suggest that successful weight management improves components of the Metabolic Syndrome in obese youth (Chang, Zhao, Li, & Yu, 2008; Harden, Cowan, Velasquez-Meyer, & Patton, 2007; King, Hobkirk, Cooke, Radley, & Gately, 2008).

There is a paucity of data examining the relationship of Metabolic Syndrome, HR, fitness, and inflammation in obese African American youth. Whether improvement in fitness, in combination with weight control, provides additive benefits in attenuating Metabolic Syndrome components has not been elucidated. Additionally, there is a paucity of data examining the effect of weight loss and fitness, alone or in combination on HRV in obese African American youth.

**Purpose**

Obesity and the Metabolic Syndrome are major public health issues that significantly threaten the health of African American youth. The health burden of obesity affects African Americans disproportionately and efficacious strategies are needed to facilitate weight management and reduce risk factors for CVD and T2DM in this population. Therefore, the purposes of this secondary data analysis were to explore the relationships among components of the Metabolic Syndrome, HRV, fitness, and inflammation in obese African American youth participating in a supervised weight management program and examine the effect of weight loss on these variables. More specifically, the following specific aims and hypotheses were addressed:

In obese African American youth, this study sought to
1. Describe the prevalence of Metabolic Syndrome components and the Metabolic Syndrome.
2. Describe HRV, fitness levels, and levels of inflammation markers.
3. Explore relationships among the presence of Metabolic Syndrome components and fitness: oxygen consumption at maximal exercise (VO2max), HRV (parasympathetic function and circadian rhythmicity), and inflammation (C-reactive protein and fibrinogen) at baseline.

   Hypotheses associated with this aim included:

3a. Higher Fitness is associated with higher HRV measures of parasympathetic function and circadian rhythmicity; Metabolic Syndrome components (lower insulin resistance [IR] and glucose, higher high density lipoprotein [HDL]-cholesterol, lower triglycerides, lower blood pressure, and lower severity of obesity); and lower levels of inflammation (C-reactive protein and fibrinogen).
3b. Inflammation is associated with the presence of the Metabolic Syndrome, higher IR, and higher severity of obesity.
3c. Lower HRV measures are associated with the presence of the Metabolic Syndrome.

In a subset of obese African American youth who completed the weight loss intervention, this study sought to address these additional aims:

4. Explore the effect of age, gender, and baseline fitness on weight loss (change in Relative Body Mass Index [RBMI]).
5. Examine the relationship among the changes in severity of obesity (change in RBMI), change in fitness (Δ VO2max), and change in HRV measures of parasympathetic function (high frequency [HF]), circadian rhythmicity (standard deviation of R-R intervals of QRS complexes of normal beats [SDNN]), and sympathetic:parasympathetic balance (LF/HF ratio).

   Hypotheses associated with this aim included:

5a. As RBMI improves HRV improves and fitness remains stable.
5b. Improvements in fitness are associated with improvements in HRV.

**Significance**

Obesity is a risk factor for a myriad of chronic diseases, including CVD and T2DM, with an estimated $129 billion dollars spent nationally on obesity, (US Department of Health and Human Services, 2001). Of this, at least $127 million is attributed to childhood obesity (Wang & Dietz, 2002). The American Diabetes Association (ADA) estimates that 1 in 6 overweight adolescents has impaired glucose tolerance (prediabetes), and these youth are at greater risk for progression to T2DM
While overt CVD is rare in youth, pathological data provide compelling evidence that atherosclerosis begins in childhood and is associated with obesity and other Metabolic Syndrome markers (Buiten & Metzger, 2000; Chu, Rimm, Wang, Liou, & Shieh, 1998; Eisenmann, 2004). The coexistence of these Metabolic Syndrome components has been well documented in epidemiologic studies of adults and children (Aldamiz-Echevarria et al., 2004; Bao, Srinivasan, & Berenson, 1996; Bao, Srinivasan, Wattigney, & Berenson, 1994). Data from the National Health and Nutrition Examination Survey (NHANES) 1999-2000 revealed that 67% of adolescents have at least one component of the Metabolic Syndrome. From 1988 to 2000, adolescents participating in the NHANES III and NHANES 1999-2000 exhibited an increased prevalence of central obesity, low HDL-cholesterol, and hypertension over time, with the Metabolic Syndrome being more prevalent in overweight compared with normal-weight adolescents (38.6% vs. 1.4%).

According to the National Cholesterol Education Program panel, the Metabolic Syndrome will soon have a greater impact on premature coronary artery disease than tobacco (Third Report of the National Cholesterol Education Program, 2001). However, traditional risk factors, including the Metabolic Syndrome, cannot explain the greater health burden of disease seen in obese African Americans. Thus it is imperative to identify additional risk factors in youth; such as HRV deterioration and increased inflammation, that may contribute to disease development or identify early indication of disease and examine the effect of weight management programs on these risk factors.

**Conceptual Framework**

This study investigated the relationships among components of the Metabolic Syndrome, inflammation, HRV (a measure of cardiac autonomic function), and fitness in obese African American youth and the effect of weight loss (based on changes in relative body mass index) on these variables. Figure 1.1 depicts the proposed relationship among these variables.

The Metabolic Syndrome, characterized by central adiposity, atherogenic dyslipidemia (elevated triglycerides and diminished high-density lipoprotein cholesterol), hypertension, IR, and glucose intolerance, is a precursor to CVD and T2DM (Lorenzo, Williams, Hunt, & Haffner, 2007). A recent study in children suggested obesity as the most substantial influence on the manifestation of these Metabolic Syndrome risk factors, as obesity often precedes hyperinsulinemia (Berenson, 2005; Nam & Marcus, 2000; Steinberger, Moorehead, Katch, & Rocchini, 1995) and adipocytes produce proinflammatory cytokines. Earlier study findings support the hypothesis that poor insulin utilization plays a role in the development of the Metabolic Syndrome (Bao et al., 1994). The World Health Organization (WHO) recognizes IR as a major mechanism for the Metabolic Syndrome, requiring IR or deterioration in glucose metabolism is present before a diagnosis of the Metabolic Syndrome can be made (Marchesini et al., 2004).
Metabolic Syndrome
Impaired GT, Hyperinsulinemia or T2DM

Plus 2 of the following:
Central Obesity
Elevated BP
Hypertriglycerides
Decreased HDL

Fitness
Inflammation
Heart Rate Variability

Weight Change

GT – glucose tolerance
T2DM – type 2 diabetes mellitus
BP – blood pressure
HDL – high density lipoprotein

Obesity has a direct effect on insulin sensitivity and triglyceride level. Increased adipose tissue results in increased free fatty acid turnover, a diminished inhibitory effect of insulin on lipolysis, and elevated triglycerides; particularly central adiposity. Severity of obesity, assessed by fat mass, has also been linked to increased levels of inflammatory markers of fibrinogen and C-reactive protein. Adipose tissue is a metabolically active endocrine organ producing a large number of hormones, peptides, and small molecules that interact with metabolic, endocrine, and immune functions. These include inflammatory cytokines, thrombotic and inflammatory markers, leptin, and vasoactive substances which contribute directly or indirectly to changes in vasculature and glucose metabolism (Eckel, Kahn, Robertson, & Rizza, 2006; Rader, 2000).

Hyperinsulinemia and IR may stimulate increased production of inflammatory molecules (McLaughlin et al., 2002) resulting in concomitant inflammation, even in the absence of obesity. Regardless of the cause of the inflammation, promotion of CVD by inflammation appears to be by decreasing insulin sensitivity and increasing arterial lipid deposits causing atherosclerosis and impaired endothelial function (Jansson, 2007; Lowe, 2001). Kressel et al. (2008) found that adults with the Metabolic Syndrome had significantly higher levels of inflammation than those without the Metabolic Syndrome. Similar findings were found in youth.

Poor insulin utilization, IR and hyperinsulinemia, increase blood pressure through sympathetic nervous system activation, renin-angiotensin system stimulation, impairment of nitric-oxide mediated vasodilation, and vascular smooth muscle cell proliferation. Further, free fatty acids may induce IR by inhibiting insulin signaling or interfering with glucose transport or metabolism.

Adipose tissue expresses inflammatory cytokines and stimulates the release of inflammatory markers, such as C-reactive protein and fibrinogen which contribute to the development of fatty streaks and atherosclerotic lesions. Additional, adipose tissue expresses vasoactive substances (renin, angiotension, angiotension-converting enzyme) which contribute to increased volume and vasoconstriction even in the absence of hyperinsulinemia. These changes in the sympathetic-parasympathetic balance are reflected in altered HRV and blood pressure.

Fitness levels have been linked to improved HRV, particularly measures of parasympathetic function, in adults and youth, with and without obesity, and convincing evidence suggests that fitness protects against the development of cardiovascular disease and T2DM, with higher fitness levels inversely associated with lower levels of inflammation (Kuo, Yen, Chen, Yu, & Bean, 2007). In youth, studies suggest that adiposity is the major determinant of inflammatory levels in children although fitness has a smaller independent effect (Cook et al., 2000; Ruiz, Ortega, Warnberg, & Sjostrom, 2007). It remains unclear whether alternations in HRV are primarily due to adiposity, IR, glucose intolerance, or fitness.

Obesity, IR, inflammation, and a combination of these factors have been proposed as the underlying mechanism for this clustering of cardiovascular risk factors known as
the Metabolic Syndrome. Research suggests that CVD and T2DM share common antecedents including obesity, IR, and physical inactivity. Further research is needed to determine whether obesity, inflammation or IR best predict the development of the Metabolic Syndrome in youth. Evaluation of the effect of weight loss and fitness on inflammation and HRV, as well the relationship of these variables with the Metabolic Syndrome, in African-American youth provides crucial information regarding how weight loss reduces risk for CVD and T2DM in this population. Given the convincing evidence that fitness is protective against the development of CVD and T2DM (Harrell, Pearce, & Hayman, 2003; Kuo et al., 2007; Pescatello et al., 2004), it is important to assess whether fitness attenuates risk factors of inflammation, Metabolic Syndrome, and HRV in obese youth.

**Major Concepts and Definitions**

Theoretical and operational definitions for the major concepts within the conceptual model include the following:

**Obesity**

Obesity is excess fat mass which causes deleterious effects (Kopelman, 2000). However, because the degree of fat mass in children varies depends upon ethnic background, gender, developmental stage and age, there is a lack of consensus regarding which measure of fat mass reflected excess fat mass in children and what cut-points to use to define obesity in youth. Until recently, there was a reluctance to categorize youth as being obese; youth were classified as being at risk for overweight or overweight rather than obese, even when measures of obesity exceeded adult cut-points.

A variety of direct and indirect measures of obesity are available for clinical and research application. Direct measurements of body fat content, such as hydrodensitometry, bioimpedance, or dual energy X-ray absorptiometry (DEXA) are useful tools in scientific studies but because of economic and time burdens are impractical for clinical use. Waist circumference, skinfold thickness and body mass index (BMI) are the most useful non-invasive clinical measures for obesity. Until recently, normative values for waist circumference were not available and skinfold measurements vary substantially between examiners, limiting the utility of these measures of obesity.

Body mass index is recommended as the preferred methods for determining obesity as it correlates well with body fat in adults (Berkis & Azari, 2005) and children (Freedman, Khan, Serdula, Ogden, & Dietz, 2006; Velasquez-Mieyer, Neira, Nieto, & Cowan, 2007). However, it is recognized that BMI does not distinguish fat mass from fat-free mass and may underestimate or overestimate fat mass. BMI is calculated by dividing the weight (kg) by the square of the height (m). Overweight and obese BMI ranges in children 6 to 18 years of age (Centers for Disease Control, 2002) are based on surveys in 6 countries, including the U.S. (Cole, Bellizzi, Flegal, & Dietz, 2000).
Obesity Severity

In adults, but not children, severity of obesity is categorized by BMI levels. Normative values for BMI vary across age groups and gender making cross-sectional and longitudinal follow-up of obesity problematic in children. To facilitate comparisons across ages and genders, a concept called relative BMI (RBMI) was introduced (Velasquez-Mieyer, Perez-Faustinelli, & Cowan, 2005). RBMI is calculated by dividing actual BMI by the BMI at the 50th percentile for age and gender and multiplying by 100 to provide a measure of obesity severity in children. Both BMI and RBMI were similarly associated with indices of glucose metabolism and insulin dynamics and cardiovascular risk factors in overweight and obese youth and both correlated with DEXA measures of fat mass in Caucasian and African-American youth (Velasquez-Mieyer, Neira, Nieto, & Cowan, 2007). For this study, RBMI was used as the measure of obesity severity.

Overweight in children is defined as a BMI between the 85th and 95th percentile, while obesity is defined as a BMI ≥ 95th percentile for age and gender. These BMI cut points are linked to adult cut points for overweight and obesity, which are good indicators of risks for adverse health outcomes (Braunschweig et al., 2005; Velasquez-Mieyer, Cowan, Neira, & Tylavsky, 2008).

Weight Loss

In adults, effective weight management is typically measured by weight loss, expressed as either pounds or kilograms, or decrease in body mass index with a 10% weight loss considered successful (Klein et al., 2004). In children and adolescents, height and weight increases throughout development until adult values are reached. Thus, adult measures of weight loss may not adequately reflect successful weight management. RBMI provides an objective way to evaluate weight changes over time in youth (Velasquez-Mieyer, Cowan, Arheart, Buffington, Spencer, & Connelly, 2003). For the purposes of this study, changes in severity of obesity (ΔRBMI) were used as the measure of weight loss.

Metabolic Syndrome

Although Metabolic Syndrome is a well-recognized clinical phenomenon, there is no internationally accepted definition in adults or children. For the current study, subjects were classified as having the Metabolic Syndrome based on criteria proposed by the World Health Organization in 2004 (Invitti et al., 2006). This definition of the Metabolic Syndrome required the presence of IR, impaired glucose tolerance or T2DM, plus two of the remaining risk factors. Other risk factors include central adiposity, high systolic blood pressure, high triglycerides, and low HDL-C. Cut-points were modified to reflect updated normative values when available. Microalbuminuria was omitted from the WHO.
definition because its significance in children is still uncertain and measurements were not available in the study population. Individual components of the Metabolic Syndrome are defined below, and criteria with measurement cut-points are shown in Table 1.1.

- Insulin resistance is the cell’s inability to utilize insulin. Insulin resistance will be calculated using the quantitative insulin-sensitivity check index (QUICKI). The correlation between QUICKI and glucose clamp studies (SI\textsubscript{Clamp}), the gold standard for assessment of IR, was comparable to that between and homeostasis model assessment (1/HOMA) and SI\textsubscript{Clamp} \((r = 0.82)\) (Chen et al., 2003). QUICKI is a simple representation of insulin sensitivity that is useful for evaluating IR. Using QUICKI, a finding of < 0.3 is equivalent to insulin resistance (Velasquez-Mieyer et al., 2008).

- Impaired glucose tolerance also is termed “prediabetes” and is recognized as a strong risk factor for the development of T2DM and CVD (American Diabetes Association, 2009). The ADA (2008) defines impaired glucose tolerance as either a fasting plasma glucose (FPG) levels ≥ 100 mg/dl but < 126 mg/dl or a 2-h postload glucose ≥ 140 mg/dl but < 200 mg/dl.

- Diabetes mellitus is a metabolic disease characterized by hyperglycemia resulting from either a defect in insulin secretion, insulin action, or both (American Diabetes Association, 2009). Based on ADA criteria, type 2 diabetes was determined by a fasting plasma glucose level ≥ 126 mg/dl or a 2-h values in the oral glucose tolerance test (OGTT) of ≥ 200 mg/dl.

- Central adiposity is visceral and subcutaneous abdominal fat mass and is measured by waist circumference. A waist circumference ≥ 90\textsuperscript{th} percentile for age and sex, based values in a nationally representative samples of African-American, European-American, and Mexican-American children and adolescents (Fernandez et al, 2004) was used as the measure of central adiposity.

- High systolic blood pressure is based upon normative blood pressure (BP) tables developed by the Task Force on High Blood Pressure in Children and Adolescents for youth less than 12 years of age. Normative values are based on age, gender and height. Youth with a BP > 90\textsuperscript{th} and < 95\textsuperscript{th} percentiles for age, gender, and height in children are classified as prehypertensive while BP values ≥ 95\textsuperscript{th} percentile are considered hypertension (Falkner and Daniels 2004). By age 12, the 90\textsuperscript{th} percentile for systolic BP exceeds 120 mmHg (adult prehypertension). Thus, adolescents with systolic blood pressure ≥120/80 mm Hg (but < 95\textsuperscript{th} percentile) are classified as having prehypertension and BP values ≥ 95\textsuperscript{th} percentile on the Task Force on High Blood Pressure in Children and Adolescent Tables are diagnostic for Hypertension. Individuals who meet the criteria for either systolic pre-hypertension or hypertension were classified as having high systolic blood pressure.

- High triglycerides. Triglycerides are derived from fats eaten in foods and are stored in fat cells for future energy needs. (American Heart Association [AHA], n.d.). High triglycerides are defined as serum triglycerides levels ≥ 90\textsuperscript{th} for age and sex. Triglyceride percentages were determined in a national sample of youth (Hickman et al., 1998).
Table 1.1  Metabolic Syndrome Criteria

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Measurement Cut-point</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin resistance</td>
<td>QUICKI &lt; 0.3</td>
</tr>
<tr>
<td><strong>OR</strong></td>
<td></td>
</tr>
<tr>
<td>Impaired glucose tolerance</td>
<td>Fasting glucose ≥ 100 mg/dl and &lt; 126 mg/dl***</td>
</tr>
<tr>
<td></td>
<td>2hPP glucose ≥ 140 mg/dl and &lt; 200 mg/dl</td>
</tr>
<tr>
<td><strong>OR</strong></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>Fasting glucose ≥ 126 mg/dl ***</td>
</tr>
<tr>
<td></td>
<td>2hPP glucose ≥ 200 mg/dl</td>
</tr>
<tr>
<td><strong>PLUS 2 of the following:</strong></td>
<td></td>
</tr>
<tr>
<td>Central adiposity</td>
<td>WC ≥ 90th percentile for age and sex*</td>
</tr>
<tr>
<td>High systolic blood pressure</td>
<td>≥ 90th percentile systolic blood pressure for age sex and</td>
</tr>
<tr>
<td></td>
<td>height; **</td>
</tr>
<tr>
<td></td>
<td>or &gt; 120/80 if 12 years of age or older **</td>
</tr>
<tr>
<td>High triglycerides</td>
<td>&gt; 90th percentile for age and sex****</td>
</tr>
<tr>
<td>Low HDL-cholesterol</td>
<td>&lt; 10th percentile for age and sex****</td>
</tr>
</tbody>
</table>

QUICKI – quantitative insulin-sensitivity check index
WC – waist circumference
• Low HDL-cholesterol. HDL cholesterol normally makes up 20 to 30 percent of cholesterol values and some evidence suggests that HDL protects against the development of atherosclerosis (NCEP). HDL cholesterol carries cholesterol to the liver, where it is removed from the body. In youth, HDL-cholesterol values below the 10th percentile for age and sex were considered low. HDL percentiles were based on values obtained from a national sample of youth.

**Inflammation**

Inflammation is the body’s reaction to injury and is believed to have a role in the pathogenesis of cardiovascular events and diabetes (Bastard, Delattre, Hainque, Brucker, & Oberlin, 1999; Bermudez & Ridker, 2002; Haffner, 2006; Tracy, 1998). Two inflammatory markers shown to have clinical utility in adult populations are fibrinogen and C-reactive protein (CRP). Mild elevations of CRP levels are predictive of coronary heart disease (Lim, et al., 2005; Ridker, Wilson, & Grundy, 2004; Sattar et al., 2003) and it may be an important precursor of T2DM and the Metabolic Syndrome (Sattar et al.; Yudkin, et al., 2000). Nakanishi et al. (2005) found CPR levels increased continuously across the spectrum of fasting glucose and CRP levels also increased as the number of Metabolic Syndrome Components increased (p = 0.003). For the purposes of this study, serum levels of CRP ≥ 1.0 mg/dl and fibrinogen ≥ 400 mg/dl were used as markers of systemic inflammation.

**Heart Rate Variability**

Twenty-four hour measures of HRV provide information regarding cardiac autonomic function during activity and rest. Frequency and time domain analyses of HRV provide measures of parasympathetic and sympathetic modulation and circadian rhythmicity. Frequency domain analysis involves power spectral density (PSD) techniques that convert variances in R-R intervals length into frequency waveforms. The high frequency (HF) component (0.15-0.40 Hertz) reflects parasympathetic neural modulation while the low frequency (LF) component (0.04-0.15 Hertz) is mediated by both sympathetic and parasympathetic modulation. The ratio of LF/HF represents sympathetic neural modulation and is considered a measure of sympathetic:parasympathetic balance. Time domain measure of SDNN (the standard deviation of R-R intervals of QRS complexes of normal beats) was used as the measure of circadian fluctuation. This study employed measures of circadian fluctuation (SDNN), parasympathetic function (HF), and sympathetic:parasympathetic balance (LF/HF ratio) to operationalize HRV.

**Fitness**

Physical fitness encompasses aerobic fitness, strength, endurance, flexibility, and body composition (Molnar & Livingstone, 2000). Aerobic fitness is specifically
recognized for its ability to predict cardio vascular disease (Farrell, Kampert, & Kohl, 1998). The “gold standard” for aerobic fitness is oxygen consumption at maximal exercise (VO\textsubscript{2max}) which reflects the ability of the cardiopulmonary system to deliver oxygen to working muscles as well as the ability of muscles to use oxygen efficiently. Graded exercise tests that progress youth to their maximal effort are suitable for evaluating aerobic fitness (defined as VO\textsubscript{2max}) in obese youth (Mitchell et al., 2002; Owens & Gutin, 1999). VO\textsubscript{2max} was measured during a cardiopulmonary exercise test with youth exercising until they achieved maximal effort. Fitness was defined in this study as VO\textsubscript{2max} expressed in mg/kg/minute.

**Assumptions**

1. Clinical and laboratory data were recorded accurately in the de-identified data set.
2. Holter monitors were worn for at least 18 hours with nighttime values recorded.
3. Subjects provided maximal effort during fitness testing; maximal effort was validated through ratings of perceived exertion and measurement of respiratory quotient.
4. The weight loss program was relevant for the study population.

**Limitations**

1. All subjects were recruited from the same geographical area, thus results may not be generalizable to other populations.
2. No uniform definition of the Metabolic Syndrome exists in children, and most have not been developed with a population of African Americans.
3. Normative values for inflammatory markers based on age and gender are not known.
4. Concomitant asthma could be a limiting factor when assessing fitness.
5. There was a wide range of ages in the study population. Age may be a confounding variable.
6. Improvements in obesity may not have been of sufficient duration or degree to affect changes in Metabolic Syndrome, inflammatory, or HRV measures.
7. The weight loss of the subjects may not reflect fat mass loss. Obesity was measured by BMI and RBMI. This measure was used because of its simplicity, economical and ease of use for the clinician, however, true fat mass was not assessed. Weight loss generally involves the loss of both fat and lean mass and it is anticipated that fat mass loss contributes to improvements in Metabolic Syndrome markers.
CHAPTER 2: REVIEW OF LITERATURE

Introduction

A review of literature relevant to the major concepts proposed in the conceptual framework is included in this chapter. The first section addresses the Metabolic Syndrome in youth including controversies associated with defining the Metabolic Syndrome in this population, normative values for each of the components of the Metabolic Syndrome and the prevalence of the Metabolic Syndrome in youth. Inflammatory and thrombotic markers, while identified as components of the Metabolic Syndrome, but often not included for diagnostic criteria of the Metabolic Syndrome, are also examined. The second section addresses physical activity and fitness recommendations for youth and research examining the relationship of Metabolic Syndrome to physical activity and fitness. The third section focuses on heart rate variability in youth and reviews research concerning the relationship of fitness, heart rate variability, and the Metabolic Syndrome in adults and youth. The final section of this chapter addresses effective weight loss programs in children and the effect of weight loss in adults and children on fitness, heart rate variability and metabolic markers.

Metabolic Syndrome

Described in 1988 as a cluster of symptoms, Metabolic Syndrome is a set of risk factors that includes: abdominal obesity, a decreased ability to process glucose, dyslipidemia, and hypertension (Reaven, 1988). More recently, cardiovascular inflammatory and prothrombotic markers, have been associated with the syndrome but are not part of the diagnoses and/or definitions ("Third Report of the National Cholesterol Education Program," 2002). There are five major definitions for Metabolic Syndrome in adults (Strazzullo et al., 2008) and many more based on these definitions that were developed by multiple researchers. The five major definitions are; The World Health Organization (Zimmet, Alberti, & Shaw, 2005), the European Group for the Study of Insulin Resistance (Ryden et al., 2007), the National Cholesterol Education Program (Grundy et al., 2005), the American Association of Clinical Endocrinologists (Einhorn, et al., 2003) and the International Diabetes Federation (Zimmet et al., 2007).

Defined by the World Health Organization in 1998, the central focus was impaired glucose tolerance, insulin resistance or diabetes (Alberti, 1998; Ramos, Baglivo, Ramirez, & Sanchez, 2001). The diagnosis was made if the patient was insulin resistant (by euglycemic clamp) and at least two of the following: obesity (WHR or BMI), hypertension (≥140/90), microalbuminuria, or dyslipidemia (TG > 150 mg/dL or HDL < 35 mg/dL for men and 39 mg/dL for women). Also included, but not essential for a diagnosis, are inflammatory markers. Because this definition was difficult to use in the clinical setting and research, the European Group for the Study of Insulin Resistance (EGIR) formulated another definition using insulin resistance, but not diabetes, as its focus (Bloomgarden, 2003). This group continued to use insulin resistance but instead of
using WHR or BMI to measure obesity, WC (men > 94 cm, women > 80 cm) was used and the cut-points for TG (> 177 mg/dL) and HDL (< 40 mg/dL).

To simplify the definition, the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults ("Third Report of the National Cholesterol Education Program," 2002) proposed a definition specifically for clinical use. This definition views the syndrome as a set of variables which are related and interrelated. Using this definition of the Metabolic Syndrome, diagnosis requires a patient have 3 of the following: central obesity (WC of men > 102 cm; women > 88 cm), hypertriglyceremia (> 150 mg/dL), low HDL (< 50 mg/dL), hypertension (≥ 135/85 mmHg) and an elevated fasting glucose (> 110 mg/dL) (de Ferranti et al., 2004).

The name “Insulin Resistance Syndrome” (IRS) was chosen by the American Association of Clinical Endocrinologists (AACE) in their definition to direct attention to the basic pathophysiology of the syndrome (Einhorn, et al., 2003). The criteria excluded persons with T2DM. The use of a specific number of components to diagnose the syndrome, as was defined by previous groups, was not considered appropriate as IRS was felt to be a continuum of risk based on the number and severity of components. The components are; some degree of glucose intolerance, abnormal uric acid metabolism, dyslipidemia, hemodynamic changes (sympathetic nervous system activity, renal sodium retention, blood pressure), prothrombotic factors, inflammatory markers and endothelial dysfunction. The AACE calculates the individual risk, or number of components. The diagnosis requires the presence of at least one of the following factors: 1) diagnosis of CVD, hypertension, polycystic ovarian disease, non-alcoholic liver disease, or acanthosis nigricans; 2) family history of T2DM, hypertension, or CVD, and history of gestational diabetes or glucose intolerance; 3) non-Caucasian ethnicity; 4) sedentary lifestyle; 5) BMI > 125.0 kg/m² and/or WC > 40 inches in men and > 35 inches in women; or 6) age > 40 years and at least two of the following criteria: triglyceride > 150 mg/dL, HDL < 40 mg/dL in men and < 50 mg/dL in women, blood pressure > 135/85 mm Hg and fasting glucose 110 to 125 mg/dl or 2-hour post glucose challenge result of 140-200 mg/dl.

Most recently, the International Diabetes Federation (IDF) has published a definition of the Metabolic Syndrome (Zimmet, Alberti, & Rios, 2005). This definition was to standardize the model for guidelines for the identification of persons at risk for diabetes and CVD and research. In this model, obesity is the central focus, using WC as the standard measure. Cut-points were derived for different ethnic groups. A diagnosis also included 2 of the following: hypertriglyceremia (> 150 mg/dL), decreased HDL (men < 40 mg/dL, women < 50 mg/dL), hypertension (> 130/85 mmHg) and/or fasting blood glucose above 100 mg/dL (Alberti, Zimmet, & Shaw, 2006).

Although the definitions are similar, the focus is different. ATP III criterion for the Metabolic Syndrome emphasizes the CV risk factors (McLaughlin, Allison, Abbasi, Lamendola, & Reaven, 2004), while AACE and WHO use insulin resistance (Alberti & Zimmet, 1998) and IDF (Ford, 2005) includes obesity. ATP III uses specific WC cut-points, WHO uses BMI and WHR, while the IDF definition provides region specific
criteria for WC and BMI values in response to ethnic differences. The differences in definitions create difficulties when comparing results across studies but it also provokes difficulty in defining the syndrome in youth, where the cardiometabolic damage begins.

**Metabolic Syndrome and Youth**

The definition for Metabolic Syndrome in children is even more confusing. In a recent review of the literature, Ford and Li (2008), found 46 different definitions of the syndrome pertaining to children. Even when using the same adult definition of Metabolic Syndrome there was a wide variance of findings. Lack of a commonly accepted model for the Metabolic Syndrome makes it difficult to define this syndrome and compare its prevalence across studies and in different populations. As in adults, there is no consensus on the type and number of components for the Metabolic Syndrome. The most frequently examined measurements include fasting insulin and glucose, blood pressure, measures of lipids, and one or more anthropometric measures. The following paragraphs present a review of the largest studies in the United States and Canada.

de Ferranti et al. (2004) used the adult version of the National Cholesterol Education Program as the basis for classification. A diagnosis of Metabolic Syndrome was made if the subjects exhibited 3 or more of the following: WC > 75th percentile for age and gender, fasting glucose > 110mg/dL, HDL < 50mg/dL (with values < 45 mg/dL used for boys aged 15 to 19 years), hypertension > 90th percentile for age, gender, and height, triglyceride ≥ 100mg/dL. Using this definition, they concluded that the prevalence of the Metabolic Syndrome in youth, at 9.2%, was similar as in adults, thus giving credibility to their classification.

Cook, Weitzman, Auinger, Nguyen, and Dietz (2003) also based their definition of the Metabolic Syndrome on the NCEP. However, the cut-points used were more stringent than de Ferranti et al. (2004) and incorporated information from the NCEP Pediatric Panel report, the updated Task Force report on the Diagnosis and Management of Hypertension in Childhood, as well as ATP III, and the American Diabetes Association statement on T2DM in children and adolescents. Using the cut-points of triglyceride > 110 mg/dL, HDL-C < 40 mg/dL (males and females), WC > 90th percentile (males and females), fasting glucose > 110 mg/dL, and blood pressure > 90th percentile for age, sex, and height, researchers found the prevalence of the Metabolic Syndrome to be 6.8% in overweight adolescents vs. 28.7% in obese adolescents.

In a cross-sectional study of 1,513 African American, Caucasian, and Hispanic teens, Goodman, Daniels, Morrison, Huang, and Dolan (2004) examined the prevalence of the Metabolic Syndrome in modified versions of the National Cholesterol Education Program Adult Treatment Panel III (NCEP) and World Health Organization (WHO) guidelines. Using the NCEP guidelines, Metabolic Syndrome was determined based on the presence of three of the five factors. Hypertension was defined as diastolic > 85 mmHg or systolic > 130 mmHg, WC > 102 cm for males and > 88 cm for females, and HDL < 40 mg/dL for males and < 50 mg/dL for females. Fasting triglycerides and glucose were considered abnormal if they were > 150 mg/dL and > 110 mg/dL.
respectfully. For the WHO definition, impaired fasting glucose, known diabetes, or hyperinsulinemia was required, plus two of the additional three parameters. For those youth who were nondiabetic, insulin levels in the top quartile were defined as hyperinsulinemia and hyperglycemia was defined as a fasting glucose > 110 mg/dL. The other criteria included hypertension, dyslipidemia [hypertriglyceridemia (≥ 150 mg/dL) or low HDL-C (≤ 35 mg/dL for males and 39 mg/dL for females)], and central obesity [high WC (> 102 cm males and > 88 cm females), or BMI > 30]. The compared estimated prevalence of Metabolic Syndrome in all subjects was vastly different, depending on which definition of the Metabolic Syndrome was used. NCEP guidelines defined 4.2% of the subjects while Metabolic Syndrome, per WHO guidelines, identified 8.4% of subjects. No race or sex differences were present for NCEP-defined Metabolic Syndrome. However, nonwhite teens were more likely to have Metabolic Syndrome by WHO criteria (RR, 1.40), and Metabolic Syndrome was more common among girls if the WHO-based definition was used (RR, 1.26). Additionally, Metabolic Syndrome was found almost entirely among obese teens, supporting obesity as the more consistent clinical correlate of Metabolic Syndrome rather than hyperinsulinemia. However, by definition, all of the subjects with the syndrome using this WHO-based definition had abnormal glucose metabolism.

Weiss and associates (2004) used a modified criteria based on NCEP guidelines from 2002 and WHO (Alberti & Zimmet, 1998). For the obesity measure, BMI scores were based on sex and age; for comparison, scores were converted to z-scores and classified as obese (z > 2.0), moderately obese (z = 2.0-2.5) and severely obese (≥ 2.5). Subjects were categorized as having Metabolic Syndrome if they met three or more of the following criteria for age and sex: obesity (BMI above the 97th percentile), triglycerides above the 95th percentile (adjusted for age, sex, and race), HDL cholesterol below the 5th percentile (adjusted for age, sex, and race), systolic or diastolic blood pressure above the 95th percentile, and impaired glucose tolerance. Impaired glucose tolerance was defined as fasting glucose greater than 140 mg/dL but less than 200 mg/dL at 2 hours. The prevalence increased directly with the degree of obesity and each component of the syndrome worsened with increasing obesity.

In 2008, Lee, Bacha, Gungor, and Arslanian (2008) examined the prevalence of the Metabolic Syndrome using the definitions proposed by Weiss and associates (2004), Cruz and associates (2004), Cook and associates (2003) and Ford (2005). These researchers found prevalence of the Metabolic Syndrome was substantially higher in those children who exhibited insulin levels in the highest quartile no matter the definition. In fact, Lee and colleagues (2008) suggested fasting insulin could be used as a clinical marker for the Metabolic Syndrome. These findings are in agreement with Lambert, Paradis, and associates (2004) who employed insulin as the basis of their definition of the Metabolic Syndrome in a population study of 2,240 children aged 9, 13 and 16 year olds, plus two of the remaining five criteria. The overall prevalence was 11.5% and there were no significant differences in age or gender. They reported that in all age-gender groups, obesity, SBP, blood sugar and TG all increased significantly with increasing insulin and HDL decreased.
In 2007, the IDF presented a definition for use in children and adolescents (Zimmet, et al., 2007). This definition of the Metabolic Syndrome may help researchers and providers interpret study results by offering a global consensus as to which components should be included. The IDF description of the Metabolic Syndrome for children retains the same laboratory values as in the definition that was asserted in the IDF definition for adults except WC. Percentiles of WC were used in the definition to compensate for variation in child development and race (Fernandez, Redden, Pietrobelli, & Allison, 2004). Children who are 6 years and younger were excluded from the definition since there was not enough data for this age-group. The IDF committee also recommended that children younger than age 10 years not be labeled with the syndrome; rather clinicians should recommend weight reduction for those children whose abdominal measurements are above the 90th percentile. For children over 10 years but under 16 years of age, the diagnosis of the syndrome is based on abdominal obesity and the presence of two or more of the following; elevated triglycerides, low HDL-cholesterol, high blood pressure, or increased plasma glucose.

Ford, Li, and Sattar (2008) used the IDF criteria in a secondary analysis to assess the prevalence of the syndrome in 2014 US children aged 12 to 17 years who had taken part in the NHANES, 1988-1994 (US Department of Health and Human Services, 1994). They found a prevalence of the Metabolic Syndrome of 4.5%. This prevalence estimate is the lowest estimate to date. However, they found risk factors for the Metabolic Syndrome included increasing age, male gender, and ethnicity. Specifically, the syndrome affected 7.1% of children aged 16 to 17 years versus 1.2% of 12 year-olds; 6.7% of boys versus 2.1% of girls. Additionally, the syndrome was present in 7.1% of Mexican-American children compared with 4.5% of White children and 3.0% of African-American children.

Definitions of the Metabolic Syndrome for the pediatric population are based on previously reported adult definitions (Cook et al., 2003; Cruz et al., 2004; de Ferranti et al., 2004; Ford, 2005; Weiss et al., 2004). Discrepancies can make comparisons of studies not just difficult but impossible. There is still no consensus as to which components to include or which component if any should be considered the foundation of the syndrome. There is no consensus regarding the values or cut points for each of the included components. The overall prevalence estimates of the Metabolic Syndrome in children range from 4.2% to 50.0%. This range can be contributed to the wide variation of definitions. The IDF Consensus Definition of the Metabolic Syndrome for Children and Adolescents (Zimmet, 2007), is the first attempt at a worldwide agreement on the definition for youth; yet, there is still controversy. However, youths with the Metabolic Syndrome are characterized by increased WC/visceral adiposity/BMI, blood pressure, insulin resistance/hyperinsulinemia, and dyslipidemia regardless of the Metabolic Syndrome criteria used.

**Normative Values for the Components of the Metabolic Syndrome in Youth**

A considerable problem in the research and clinical application of the concept of Metabolic Syndrome in adults as well as children is not only many definitions of the
syndrome, but the many variations in the definitions of the components. The following section is a literature review of the values of the various components of the Metabolic Syndrome as it relates to youth.

**Obesity.** Obesity is defined as an excessive accumulation of body fat. Not all obese infants become obese children, and not all obese children become obese adults. However, the prevalence of obesity increases with age among both males and females (Lohman et al., 1999), and there is a greater likelihood that obesity beginning in childhood will persist through the life span (Epstein, Koeske, Wing, & Valoski, 1986). According to (Ogden, Carroll, & Flegal, 2003), obesity has become the most prevalent pediatric disorder this trend continues to grow. The National Center for Health Statistics (CDC, 2002) reported that 15.5% of children and 15.3% of adolescents were overweight. Just two years later the estimates of overweight children and adolescents from NHANES 2003-04 found 18.8% of children (6 to 11 yrs) and 17.4% of adolescents (12 to 19 yrs) were overweight (Ogden et al., 2006), with significant increases among girls (13.8% to 16.0%) and boys (14.0% to 18.2%). Obesity among race or ethnic groups was found to have significant differences. The prevalence of overweight in Mexican-American and non-Hispanic black girls was higher than among non-Hispanic white girls (Freedman, et al., 2006). Among boys, the prevalence of overweight was significantly higher among Mexican Americans than among either non-Hispanic black or white boys. There were significant differences by age as adolescents were more likely to be overweight than younger children (Freedman et al., 2006).

Anthropometry is one of the most basic tools for assessing nutritional status, whether overnutrition or undernutrition. A variety of methods are available to measure body fatness and body thinness (de Onis, 2004). Commonly used techniques for the accurate estimation of body fatness include underwater weighing, dual energy X-ray absorptiometry (DXA), total body water, total body electrical conductivity (Goran, 1999), total body potassium (Schaefer, Georgi, Wuhl, & Scharer, 1998), and computed tomography (Vade, Agrawal, Lim-Dunham, & Hartoin, 2002). However, because of their complexity and cost, the use of most of these methods is limited to research settings. The most frequently used tools in research and clinical screening are anthropometric-based measurements such as skinfold-thickness or waist circumference (WC) measurements or various height- and weight-based indexes such as weight-for-height, body mass index. The following is a description of the anthropometry tools used to measure the cohort in this study.

**Body Mass Index (BMI).** BMI is calculated as weight divided by the square of height measured in meters (kg/m²) and is recommend because; it is easily obtained, correlates strongly with body fat percentage, is associated only weakly with height, and it identifies the fattest individuals correctly (Freedman et al., 2004; Himes & Dietz, 1994; Koplan et al., 2005; Krébs & Jacobson, 2003). In adults the absolute BMI cut-points of 25 kg/m² and 30 kg/m² are used almost universally to define overweight and obesity (Bjorntorp, 1998; Borecki et al., 1998; Kuczmarski, Carroll, Flegal, & Troiano, 1997). These BMI cut-points were based on evidence of increasing mortality above a BMI of 25 kg/m², with even greater increases above 30 kg/m² (Borecki et al., 1998). There is not an
accepted definition of obesity in children, and the childhood classification is based solely on the distribution of sex- and age-specific BMI levels in national studies. Use of BMI to assess body weight in children requires growth and gender considerations, as children’s development varies with age and gender. Thus the BMI values for children and youth are specific to both (Cole, et al., 2000). The International Obesity Task Force proposed that child body mass index percentiles cut-points be linked to adult cut-points (Bellizzi & Dietz, 1999; Dietz & Robinson, 1998). The values of these cut-points was obtained by averaging data from youth in Brazil, Great Britain, Hong Kong, Netherlands, Singapore, and the United States between 2 and 18 years by gender (Cole et al., 2000). For the Centers for Disease Control (CDC) and NHANES (Chumlea et al., 2002; Roberts & Dallal, 2001), two levels of overweight are used: the 85th percentile, as an "at risk" level, and the 95th percentile, as the overweight point (Barlow & Dietz, 1998; Cook, et al., 1994; Kuczynski, et al., 2000; Montague, 2003). The Institute of Medicine defines children with a BMI of > 95th percentile for age and gender as obese to emphasize the seriousness, urgency, and medical nature of obesity in children (Koplan, et al., 2005). Krebs et al. (2007) endorsed this position and recommended that a BMI of > 85th percentile but < 95th percentile be considered “overweight,” replacing the term “at risk of overweight” held by the CDC (Centers for Disease Control, 2000) and NHANES (Chumlea et al.; Hakeem, 2001). The American Obesity Association uses the 85th percentile of BMI as overweight and the 95th percentile for obesity. The 95th percentile was chosen based on a corresponding BMI of 30, the marker for obesity in adults. The 85th percentile corresponds to the overweight reference point for adults, which is a BMI of 25 (Lyznicki, Young, Riggs, & Davis, 2001). Importantly, all definitions are strong predictors of metabolic complications, including a poor lipid profile and increased blood pressure and insulin resistance in young adulthood and the predictive ability of both is comparable (Janssen et al., 2005).

The determination of adiposity status is challenging as BMI and WC change considerably with normal growth and maturation in addition to adiposity, RBMI is used to combat this challenge Relative BMI is a concept used in research to adjust for growth in children (Velasquez-Mieyer et al., 2003) To calculate this measure, the calculated BMI is divided by the BMI for the 50th percentile for age and gender and multiplied by 100. Using RBMI allows comparisons across age and gender groups, which is especially important in this study where the age spans from 7 to 18 years old.

Waist Circumference (WC). Though BMI is associated with the clustering of CVD risk factors, including dyslipidemia, hypertension, and insulin resistance, WC has been recommended as a means of identifying persons with central adiposity (Taylor, Jones, Williams, & Goulding, 2000), and therefore more predictive of CVD risk (Katzmarzyk et al., 2001). Using MRI, Brambilla and associates (2007) compared BMI and WC in children with VAT and found WC provides a better estimate of VAT (65% vs. 56% of variance), whereas BMI was better at estimating subcutaneous adipose tissue (89% vs. 84% of variance). WC is significantly more efficient than BMI in predicting insulin resistance, blood pressure, serum cholesterol levels, and triglyceride levels (Lee, Bacha, & Arslanian, 2006; Maffeis, Grezzianni, Pietrobelli, Profera, & Tato, 2001). This may indicate that WC measurements provide different information than BMI. However,
Moreno et al. (2002), found no differences of BMI, WC, or skinfold measurements in the identification of the Metabolic Syndrome in a cohort of Spanish children, as did Katzmarzyk and colleagues (2004) in a cohort of African American and Caucasian boys. Sarria and colleagues (2001) did not find a significant difference in the capability of WC percentile cut-points to identify the most obese boys compared to triceps skinfold or BMI percentiles. Hirschler, Calcagno, Aranda, Maccallini, and Jazdinsky (2007) reported no statistically significant difference in the ability of WC or BMI z-score to predict Metabolic Syndrome in 5,103 children 4 to 13 years of age. However, they used a WC threshold of ≥ 75th percentile to predict Metabolic Syndrome. Morimoto and colleagues (2007) investigated whether BMI could predict WC. After controlling for age and sex; a linear relationship was found. The correlation was strong in boys 9-10 years old (r = 0.940, p < 0.001) and in 12-13 years old (r = 0.880, p < 0.001), with similar findings in girls 9-10 years old (r = 0.933, p < 0.001) and 12-13 years old (r = 0.859, p < 0.001).

WC has been used as a measure of central obesity and visceral adipose tissue (VAT) in children and adults and linked to health risks and metabolic disorders (Gower, Nagy, Trowbridge, Dezenberg, & Goran, 1998; Katzmarzyk, 2004). There are studies regarding which measure is a better estimate of obesity and the better predictor of risk for CVD, T2DM and Metabolic Syndrome. These studies suggest that BMI and WC could be interchangeable for obesity measure in the Metabolic Syndrome definitions.

The results of a cross-sectional study of 9,713 youth ages 2 to 18 years was used to describe and provide estimates of the distribution of WC according to percentiles in African American, European-American, and Mexican-American children, and to test for group differences at different percentiles (Fernandez, Redden, Pietrobelli, & Allison, 2004). The results were used to determine reference cut-point percentiles for age, gender and race.

**Lipid Profile.** Normal lipid values for children are defined according to percentile cut points within population distributions. In large population-based samples, NCEP (Expert Panel on Blood Cholesterol Levels in Children and Adolescents, 1992) has published a single set of cut points for children and adolescents ages 2 to 19 years. These values can be used to identify those with abnormal lipoprotein levels of total cholesterol (TC), low density lipoprotein (LDL) cholesterol, HDL cholesterol, and triglycerides (American Academy of Pediatrics [AAP], 1992).

As a source for identifying children and adolescents at high-risk of CVD, these values have been accepted by the AHA (Kavey, 2000; Kavey et al., 2003) and the American Academy of Pediatrics (Daniels & Greer, 2008). However, these cut points do not take into account age- and sex-specific differences that have been shown to occur with normal development (Berenson, Srinivasan, Frerichs, & Webber, 1979; Freedman, Bowman, Otvos, Srinivasan, & Berenson, 2000; Glikson, Dwyer, & Wlodarczyk, 1990). For instance, TC levels increase from birth, stabilize at approximately age two years, peak prior to puberty, then decline slightly. NCEP recommendations are based on results from the Lipid Research Clinics (LRC) Prevalence Study, which determined the 95th percentile cut point for TC as 200mg/dL and for LDL-C as 130 mg/dL. As a result,
Jolliffe and Janssen (2006) have proposed new lipoprotein cut points for adolescents 12 to 19 years of age based on combined data from 3 National Health and Nutrition Examination Surveys (NHANES III 1988-94, NHANES 1999-2000 and NHANES 2001-2002). These cut points were derived with the use of age- and sex-specific growth curves that were linked to adverse adult lipoprotein thresholds established by the NCEP Adult Treatment Panel (Expert Panel on Blood Cholesterol Levels in Children and Adolescents, 1992).

Hyperlipidemia is a risk factor for CVD (Whitworth, 2003) and T2DM (Pambianco, Costacou, & Orchard, 2007). Studies support the notion that atherosclerosis begins in childhood and progresses during adolescence and young adulthood (McMahan et al., 2006). Data from the Bogulusa Heart Study (Freedman, Dietz, Srinivasan, & Berenson, 1999) supports the relationship between obesity and hyperlipidemia; specifically low HDL and elevated triglycerides in children.

**Blood Pressure.** Overweight children were more likely to have an elevated systolic blood pressure (SBP) compared to their peers (Freedman et al., 1999), 2% in those with BMI < 5\textsuperscript{th} percentile compared with 11\% of children in the ≥ 95\textsuperscript{th} percentile (Sorof, Turner, Franco, & Portman, 2004). Using the Joint National Committee on Prevention, Detection and Treatment of High Blood Pressure guidelines for children, Young-Hyman, and associates (Young-Hyman, Schlundt, Herman, De Luca, & Counts, 2001) evaluated the risk represented by blood pressure data obtained from 137 overweight and obese African-American children aged 5 to 10 years. Eight percent of the subjects already had borderline or high systolic blood pressure (SBP) and 2\% were borderline or high diastolic blood pressure (DBP). Again using the data from NCEP, in a cohort of 1513 adolescents age 12-19, Goodman et al. (Goodman, Dolan, Morrison, & Daniels, 2005) found that hypertension was 4 times more prevalent in the obese group as opposed to the group of adolescents who were merely overweight. These studies support the positive correlation of blood pressure and obesity in children (Freedman et al., 1999; Goodman et al., 2005; Sorof et al., 2004; Young-Hyman et al., 2001).

Blood pressure rises as children age (Falkner & Daniels, 2004), thus normative values for blood pressure in children < 12 years are based on age, gender and height (Falkner & Daniels, 2004). For children > 12 years, the adult values are used. HTN is defined as ≥ 95\textsuperscript{th} percentile SBP or DBP (Falkner & Daniels, 2004), however by age 12, the 90\textsuperscript{th} percentile for systolic BP exceeds 120 mmHg (adult prehypertension) thus, adolescents with systolic blood pressure ≥120/80 mm Hg (but < 95\textsuperscript{th} percentile) are classified as having prehypertension. Many studies of Metabolic Syndrome in children therefore use the blood pressure value at the 90\textsuperscript{th} percentile as a cut-point for elevated blood pressure (Cook et al., 2003; Cruz & Goran, 2004).

**Impaired Glucose Tolerance.** In 1997, an International Expert Committee reexamined the classification and diagnostic criteria of diabetes, which were based on the 1979 publication of the National Diabetes Data Group and subsequent WHO Study Group (1985). As a result the Committee recommended several changes (Diabetes Care, 1997). Change occurred again in 2003 when the Expert Committee on the Diagnosis and
Classification of Diabetes Mellitus concluded that impaired fasting glucose (IFG) was defined as glucose levels of 100 to 125 mg per dL and impaired glucose tolerance (IGT) should be defined as 2-hour glucose levels of 140 to 199 mg/dL on the 75-g oral glucose tolerance test (McLaughlin, Allison, Abbasi, Lamendola, & Reaven, 2004). These glucose levels are above normal but below the level that is diagnostic for diabetes. The committee concluded that patients with this level of IGT or IFG have a significant risk of developing diabetes and therefore should be targeted for prevention. It is still unclear which glucose threshold should define impaired glucose or prediabetes, as it relates to evidence of the cardiovascular effect. Studies have examined the 2003 IFG cut points and its predictive capacity for CVD in adults, and none have demonstrated an increased risk (Blake et al., 2004; Sorkin, Muller, Fleg, & Andres, 2005; Tai et al., 2004). For example, Levitzky and associates (2008) compared the 1997 and 2003 American Diabetes Association (ADA) definitions of IFG to predict CVD using the cohorts from the Framingham Offspring Study. For the 2003 IFG definition, the Odds Ratio (OR) for CHD among women was 1.7, whereas for the 1997 IFG definition, the OR for CHD in women was 2.2, which was almost as high as for women with diabetes (OR 2.5). For CVD, only the 1997 IFG definition yielded significantly greater odds of CVD in women (OR 2.1). Men were not at increased odds of developing CVD or CHD by either definition of diabetes (1997 criteria: OR = 3.0 and 2003 criteria: OR = 2.9). However, Rijkelijkhuizen and colleagues (2007) found in their comparison study of the 1997 criteria versus the 2003 criteria, that there was no significant increased risk for CVD for men unless the participants had developed diabetes.

In children, the obesity epidemic in the United States has been accompanied by an increase in the prevalence of T2DM. A multiethnic cohort of 167 obese children and adolescents measuring 2hGTT (Sinha et al., 2002) found IGT was detected in 25% of the 55 obese children (4 to 10 years of age) and 21% of the 112 obese adolescents (11 to 18 years of age) and previously undiagnosed T2DM was identified in 4% of the obese adolescents. Insulin levels were markedly elevated after the OGTT test in subjects with IGT but not in adolescents with diabetes. After controlling for BMI, IR was the best predictor of IGT (Sinha et al., 2002).

**Insulin Resistance.** Obesity and lack of exercise tend to lead to IR and IR has a negative effect on lipid production; increasing LDL, and TG levels in the bloodstream and decreasing HDL. This can lead to fatty plaque deposits in the arteries which, over time, can lead to CVD, blood clots, and strokes. Insulin resistance also leads to increased circulating insulin and glucose levels; which increases sodium retention by the kidneys, leading to increased blood pressure and eventually hypertension. Chronically elevated glucose levels damage blood vessels and organs, such as the kidneys, and may lead to diabetes. There are different methods to measure IR; these different measures may provide differing correlational results in examining the Metabolic Syndrome components.

Examining obesity and IR, 137 obese African-American children between the ages of 5 and 10 years were given 2hGTT (Young-Hyman et al., 2001), IR was characterized by HOMA. The researchers found that the subject’s BMI accounted for 41% of the variance in HOMA. Wilkin and others (Wilkin et al., 2004) found similar
results in their longitudinal study of 307 healthy children. Measuring height, weight, BMI and HOMA-IR at the start of the school year and again at 12 and 24 months, IR was correlated with weight (girls $r = 0.33$, $p < 0.001$, boys $r = 0.18$, $P = 0.03$).

**Inflammation.** Also seen with Metabolic Syndrome but not included with the ATP III criteria are prothrombotic and proinflammatory tendencies. While these combined criteria and risk factors do not usually cause overt symptoms, they are a warning of an increased likelihood of atherosclerosis, CAD, CVA (cerebral vascular accident), diabetes, and kidney disease. Adipose tissue produces interleukin-6, a stimulator of C-reactive protein (CRP) synthesis in the liver (Tracy, 1998; Yudkin et al., 2004). CRP is one of the acute phase proteins that increase during systemic inflammation. It’s been suggested that testing CRP levels in the blood may be an additional way to assess cardiovascular disease risk.

The degree of obesity correlated with inflammatory proteins (CRP and fibrinogen), lipids, uric acid, and BP in a study of 710 obese children age 6-18 years of age (Invitti, Guzzaloni, Gilardini, Morabito, & Viberti, 2003). BMI was correlated ($p < 0.001$) with CRP ($r = 0.207$), fibrinogen ($r = 0.179$), uric acid ($r = 0.260$), TG ($r = 0.126$), HDL ($r = -0.190$), SBP ($r = 0.167$), and DBP ($r = 0.120$). They did not find a correlation between the number of components of the Metabolic Syndrome present in their subjects and CRP and fibrinogen. They also reported uric acid levels were associated with IR ($r = 0.139$, $p < 0.001$) and WC ($r = 0.335$, $p < 0.001$) (Invitti et al., 2003). Uric acid levels also increased as the number of Metabolic Syndrome components increased in the individual. The authors called for uric acid to be considered another biomarker for risk screening in children based on these results (Invitti et al., 2003).

When comparing the components of the Metabolic Syndrome to cardiac risk factors; fatness, measured as BMI or WC, was the major independent predictor of CRP in a young adult population, suggesting obesity as a mediator of excess CRP found in Metabolic Syndrome (Patel et al., 2006). Aronson and associates (2004) investigated the relationship between C-reactive protein and components of the Metabolic Syndrome. CRP levels were elevated in 3, 7, and 15% of subjects who were normal weight, overweight, and obese, respectively. Subjects with obesity had higher CRP levels compared to patients without obesity, regardless of whether they had the Metabolic Syndrome. However, there was no significant difference in CRP levels between nonobese subjects without the Metabolic Syndrome and subjects in whom the diagnosis of the Metabolic Syndrome was based on criteria other than obesity. Also, CRP levels did not differ among obese subjects with and without the Metabolic Syndrome. There was a positive correlation in CRP levels and the number of Metabolic Syndrome components, which was significantly reduced after controlling for BMI. Stepwise multivariate linear regression analysis identified BMI, triglyceride levels, HDL cholesterol levels (inversely), and fasting glucose as independently related to CRP levels. However, BMI accounted for 15% of the variability in CRP levels, whereas triglycerides, HDL cholesterol and fasting glucose levels accounted for about 1% of the variability in CRP levels.
Fibrinogens, CRP, interlukin-6 and adiponectin have been found in the adult population as antecedent to CVD. In a study of 293 obese youth, Weiss, et al (2004) found adiponectin levels decreasing with increasing obesity and IR and negatively correlated with CRP ($r = 0.18$, $p = 0.005$). Interlukin-6 increased with the degree of obesity and were correlated with CRP ($r = 0.37$, $p < 0.001$) but not with the degree of IR. Given the previous data, it was not surprising that adiponectin levels were negatively correlated with CRP ($r = 0.19$, $p < 0.001$).

Prevalence of the Metabolic Syndrome

In the U.S. it is estimated that 20% of adults (about 47 million) have Metabolic Syndrome, with the prevalence approaching 50% in elders. It can affect anyone at any age, but it is most frequently seen in those who are significantly overweight (with most of their excess fat in the abdominal area) and inactive. In children, the rise of the Metabolic Syndrome is impressive. Performing analysis of data on 991 adolescents (aged 12 to 19 years) from the National Health and Nutrition Examination Survey (NHANES 1999-2000), Duncan and colleagues (Duncan, Li, & Zhou, 2004) used the definition of the Metabolic Syndrome of the National Cholesterol Education Program (ATP III) definition modified for age to investigate the change in prevalence for this age group. The overall prevalence of a Metabolic Syndrome increased from 4.2% in NHANES (1988-1992) to 6.4% in NHANES (1999-2000). The syndrome was more prevalent in male than female adolescents (9.1% vs. 3.7%) and was found in 32.1% of overweight adolescents (BMI $\geq$ 95th percentile for age and sex), compared with 7.1% of adolescents at risk for overweight (BMI between 85th and 95th percentiles).

de Ferranti and colleagues (2004) used the NHANES III data set information (1988-1994) from children aged 12 to 19 years to test their definition of Metabolic Syndrome in children. Mexican-Americans, followed by non-Hispanic whites, had a greater prevalence of Metabolic Syndrome compared with non-Hispanic blacks (12.9%, 10.9% and 2.5%, respectively). Nearly one third (31.2%) of overweight/obese adolescents had Metabolic Syndrome.

Cook, Weitzman, Auinger, Nguyen and Dietz (2003) and Cook et al., (2003) were first to publish the prevalence of Metabolic Syndrome in adolescents. Using the data set from NHANES (1988-1994), the researchers investigated the prevalence of the Metabolic Syndrome in 2430 subjects, age 12 to 19 years using the NCEP definition. The Metabolic Syndrome was found in 4.2% of subjects with 6.1% of males and 2.1% of females being affected. The syndrome was present in 28.7% of overweight adolescents (BMI $\geq$ 95th percentile) compared with 6.8% of at-risk adolescents (BMI, 85th to < 95th percentile) and 0.1% of those with a BMI below the 85th percentile. Using a definition modified from ATP III, the researchers found 9.2% of the subjects qualified as having Metabolic Syndrome. In a population study of 8 to 17 year olds (N = 745), the prevalence was 3.6% by Srinivasan, Myers, and Berenson, 2002) using 4 criterion variables.
To determine prevalence of Metabolic Syndrome among adolescents by using definitions from the NCEP and WHO guidelines, Goodman and colleagues (2004), reported on a school-based, cross-sectional study of 1513 black, white, and Hispanic adolescents. Overall, the prevalence of Metabolic Syndrome was 4.2% defined with NCEP guidelines and WHO-defined Metabolic Syndrome was 8.4%. Metabolic Syndrome was found almost solely among obese subjects, for whom prevalence of Metabolic Syndrome by NCEP guidelines was 19.5% and was 38.9% by the WHO definition. Obviously there is poor agreement for finding Metabolic Syndrome using these criteria, and NCEP guidelines appear to find the greatest number likely to be diagnosed with the syndrome. However it is interesting to note that there was no race or sex differences were present for NCEP-defined Metabolic Syndrome but nonwhite teens were more likely to have Metabolic Syndrome by WHO criteria and Metabolic Syndrome also was more common among girls if the WHO-based definition was used. In a multiethnic, multiracial cohort of youth (N = 490) between the ages of 4-20 years, and using the NECP guidelines modified for children Weiss (Weiss et al., 2004) found the rate of Metabolic Syndrome in moderately obese children to be 39% and a rate of 49.7% in the severely obese.

In overweight or obese Hispanic children (N = 126) ages 8-13, Cruz and associates (Cruz et al., 2004) reported that 30% met the criteria for Metabolic Syndrome. In African- American youth, Braunschweig and colleagues (2005) found the prevalence of Metabolic Syndrome in 5.6% of all participants, in 13.8% of participants with BMIs at or above the 95th percentile, and in 0% of participants with BMIs below the 85th percentile. Researchers in China found the prevalence for Metabolic Syndrome in 348 overweight children (7 to 16 years of age) to be 10.3% but 22.1% for the most overweight (Fu et al., 2007).

An expert panel designated as the Pediatric Metabolic Syndrome Working Group (PMSWG) and sponsored by National Institute of Child Health and Human Development (NICHD), the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDKD), National Heart, Lung, and Blood Institute (NHLBI) and National Institutes of Health Office of Rare Diseases (NIH) has been tasked not to come to a consensus as to a definition of the Metabolic Syndrome, but to determine the potential to create a common pediatric research threshold for each of the five traditional risk components in the Metabolic Syndrome (Huang, 2008). Work of the PMSWG is continuing and thus far, articles advocating for the development of a standard pediatric definition of the Metabolic Syndrome (Ford & Li, 2008) and that a set of standardized criteria be defined as a useful paradigm in research and practice have been published (Cook, Auinger, Li, & Ford, 2008; Lee et al., 2008; Shaibi & Goran, 2008). Huang, Nansel, Belsheim, and Morrison (2008) and Maffeis, Banzato, and Talamini (2008) support the notion that inclusion of multiple metabolic variables in childhood can improve the predictive value for adult Metabolic Syndrome, and identifying children who are at risk. This would allow for better targeted prevention tactics (Morrison et al., 2008; Sun et al., 2008).

25
Conclusion

Definitions of the Metabolic Syndrome in children are based on the many and varied adult definitions. Therefore, the resulting research information of Metabolic Syndrome in young people is also many and varied. Using different definitions also does not allow comparisons among studies. Furthermore, a child’s development varies with age, and gender thus these confounding variables must also be taken into account when defining the components of the Metabolic Syndrome in youth. Additionally, the role of race and ethnicity appears to be emerging as factors for consideration. Regardless of what definition is used for diagnosis, all of the factors associated with Metabolic Syndrome are interrelated and appear to have interacting effects.

Heart Rate Variability

It is important to understand whether an alteration of HRV is one pathway through which cardiovascular health is influenced by lifestyle factors such as physical activity, fitness and fatness. Some adult studies have shown favorable HRV profiles to be related to PA and CVF, but not all. Some HRV and obesity studies have found that those obese patients have relatively poor HRV but improved with weight loss. The association strengths vary.

Heart rate variability is an important quantitative marker of cardiovascular regulation by the autonomic nervous system. Its significance was first appreciated over 40 years ago, when it was discovered that fetal distress is associated with appreciable changes in heart rate variability before any change in heart rate (Huey, Paul, Hadjie, Jilek, & Hon, 1979). Loss of heart rate variability is an independent predictor of mortality after an acute myocardial infarction (Bigger, Rolnitzky, Steinman, & Fleiss, 1994; Kitney & Rompelman, 1980; Kleiger, Miller, Bigger, & Moss, 1987; Malik, Cripps, Farrell, & Camm, 1989), is indicative of ventricular dysfunction in patients with congestive heart failure (Bilchick et al., 2002; Ponikowski et al., 1997) and is an indicator of poor prognosis in those with T2DM (Carnethon et al., 2006; Wheeler, Ahroni, & Boyko, 2002).

Autonomic Nervous System

Heart rate variability (HRV) refers to the beat-to-beat alterations in heart rate and is a measure of the function of the autonomic nervous system (Cowan, 1995). It refers to the regulation of the sinoatrial node, the natural pacemaker of the heart by the sympathetic and parasympathetic branches of the autonomic nervous system. However, because HRV is a cardiac measure derived from the EKG, it is not possible to distinguish reduced vagal activity from the brain, from reduced peripheral activity of the target organ such as the heart, specifically the SA node. Under resting conditions, the EKG of healthy individuals exhibits periodic variation in R-R intervals. This rhythmic phenomenon, known as respiratory sinus arrhythmia (RSA), fluctuates with the phase of respiration.
That is, the heart accelerates during inspiration, and decelerates during expiration. RSA is predominantly mediated by parasympathetic efferent activity to the heart: vagal efferent traffic to the sinus node occurs with expiration and is absent or attenuated during inspiration. Because of this HRV is regarded as an indicator of the activity of autonomic regulation of circulatory function. In adults, reduction of HRV has been reported to be associated with various pathologic conditions like hypertension, obesity (Festa, D'Agostino, Hales, Mykkanen, & Haffner, 2000), systemic inflammation (Carney et al., 2007; Gonzalez-Clemente et al., 2007) and hyperinsulinemia (Emdin et al., 2001). It has also been found as a predictor of mortality after an acute myocardial infarction, congestive heart failure (de Ferrari et al., 2007; Kleiger et al., 1987; La Rovere, Bigger, Marcus, Mortara, & Schwartz, 1998), end-stage renal disease (Cashion, Cowan, Milstead, Gaber, & Hathaway, 2000; Hathaway et al., 1998), and perhaps type 2 diabetes (Ziegler et al., 2008). HRV is usually calculated by analyzing the time series of beat-to-beat intervals from EKG or arterial pressure tracings. The assumption, when HRV is assessed, is that the beat-to-beat fluctuations in the rhythm of the heart provide an indirect measure of cardio-vascular health, as defined by the degree of balance in sympathetic and vagus nerve activity. Therefore, decreased HRV is considered not only a marker of impaired vagal activity of the heart but complete autonomic impairment, strongly associated with the degree of myocardial damage. Reduced HRV has thus been used as a marker of reduced vagal activity.

Measuring HRV

Heart rate variability (HRV) is a measure of variations in the heart rate. The measures of heart rate variability have been subdivided into time domain, frequency domain, and phase domain measures (Clarke & Ewing, 1982). In this study only time and frequency domain measures will be used. Studies in children are limited and generally are regarding the changes brought on by physical activity (Brunetto, Roseguini, Silva, Hirai, & Guedes, 2005; Leicht & Allen, 2008; Vinet, 2005), diabetes (Chen, Lee, Chiu, & Jeng, 2008; Faulkner, Hathaway, Milstead, & Burghen, 2001) or congenital heart disease (Kucukosmanoglu, Ozbarlas, Birand, & Kudaiberdieva, 2002; Wyller et al., 2008), traumatic brain injury (King, Lichtman, Seliger, Ebert, & Steinberg, 1997) and renal failure (Di Leo et al., 2004).

Time Domain

The gold standard for time domain measures is to examine a 24-hour assessment of HRV that has been recorded with a Holter monitor. The time domain measures are based on the amount of time, in milliseconds, in the beat-to-beat intervals of the heart or from the differences between the normal beat-to-beat intervals. The beat-to-beat interval is defined as the time in milliseconds between normal R to R waves on an EKG. The standard deviation of the normal RR interval (SDNN) is one of the most important and clinically meaningful time domain measures. The time domain measure SDNN (standard deviation of all normal to normal electrocardiographic intervals) measures low frequency
changes representative of sympathetic activity and HF measures parasympathetic activity (Galeev et al, 2001) The ratio of low to high frequency power (LF/HF) is used to measure sympathetic to parasympathetic balance (Goto et al 1997).

**Frequency Domain**

Frequency domain measures of HRV provide information on the frequency distribution of the components of HRV using power spectral density analysis. (Akselrod et al., 1981) introduced power spectral analysis of HRV for quantitative evaluation of cardiovascular autonomic control. The use of HRV analysis has increased our understanding of the influence of autonomic influence on the heart (Hayano et al, 1991; Malliani et al, 1991; Pomeranz et al, 1985). Spectral analysis of HRV is characterized by four main components: the high frequency (HF) component (.15Hz -.40Hz) measures the influence of the vagus nerve in modulating the sinoatrial (SA) node. The low frequency (LF) component (.04Hz-.15Hz) provides an index of sympathetic effects on the heart, particularly when these are measured in normalized units. The very low frequency (VLF) component (.003Hz -.04HZ) reflects the influence of several factors on the heart, including chemo receptors, thermo receptors, the renin-angiothensin system, and other non-regular factors. Almost all of the variability from a short-term spectral analysis of HRV is captured in these three components. An ultra low frequency (ULF) component (5.003 Hz) can also be observed in the HRV spectrum of a long sample. Unfortunately, a clear interpretation of the ULF component is not yet available. During the 24-hour recording of HRV, approximately 90% of variability in the heart's rhythm will be distributed within the ULF and VLF. In adults, HRV appears to be useful for identifying early manifestations of these conditions and for quantifying the rate of disease progression and the efficacy of therapeutic interventions. (Saul, 1988; Swartz, 1991) The importance of studying HRV in children and adolescents is inherent in the findings of the HRV studies in adults.

**HRV in Children**


**Diabetes, Insulin Resistance, and HRV in Children**

In a 1999 study Massin et al. found that HRV was affected by diabetes. They noted that even with good metabolic control HRV was significantly reduced in a population of children with Type 1 diabetes (ages 3-18, N = 73). This was also true in
studies by Faulkner et al. (2001) and Wawryk et al. (1997). Adolescents with type 2 DM had poorer frequency domain measures of HRV in comparison to those with type 1 DM. On the other hand, in this same study, comparing the HRV of adolescents with type 1 DM and type 2 DM, Faulkner et al (2005), observed that no matter the type of DM, females, those with higher BMI, poorer metabolic control, and lower amounts of physical activity tended to have lower levels of exercise endurance.

In overweight adolescents (Quilliot, Bohme, Zannad, & Ziegler, 2008) enhanced sympathovagal balance (sympathetic predominance) has been associated with IR. Bekezin, Kozlova, Kozlova and Igolkina (2008) found that the severity of impairment of HRV components in children and adolescents with obesity depended on the level of IR. Other recent studies in children support the association between an altered sympathovagal balance and hyperinsulinemia (Syme et al., 2008). HRV levels were also significantly lower in youth with stable type 1 DM and are asymptomatic of disease complications as compared to controls (Faulkner, Hathaway, Milstead, & Burghen, 2001; Massin et al., 1999; Wawryk, Bates, & Couper, 1997). Diminished HRV has been reported in youth with diabetes (Faulkner, Hathaway, Milstead, & Burghen, 2001) and IR and found negative associations between HbA1c and sympathetic modulation (LF) in adolescents ($r = -.324, p = .025$) with diabetes.

**Obesity and HRV in Children**

To demonstrate that obesity alters sympathetic and/or the parasympathetic modulation (Nagai, Matsumoto, Kita, & Moritani, 2003) observed 42 obese and 42 non-obese school children matched in age, gender, and height. In the obese children there was significantly LF power ($6.16 \pm 0.12$ vs. $6.42 \pm 0.05, p < 0.05$) and HF power ($5.84 \pm 0.15$ vs. $6.34 \pm 0.07, p < 0.01$) compared with the non-obese children. Furthermore, among the obese children, there was a negative correlation of LF and HF with the duration of obesity independent of age (LF: $r = -0.55, p < 0.001$; HF: $r = -0.40, p < 0.01$). Whether the duration of obesity is a factor promoting obesity or is a product of obesity remains speculative.

**Hypertension and HRV in Children**

Increased sympathetic (Sorof & Daniels, 2002) and reduced parasympathetic (Gutin, et al., 2000) tone has been linked to hypertension in obese youth. Urbina, Bao, Pickoff, and Berenson (1998) found a trend toward higher sympathetic and lower parasympathetic measures occurring in adolescent males with higher diastolic blood pressure (DBP > 85th percentile for height, age and gender). Other studies in children support the association between an altered sympathetic-vagal balance and hypertension (Guizar, Ahuatzin, Amador, Sanchez, & Romer, 2005; Lin et al., 2008), but the children in these studies who were hypertensive also tended to be overweight or obese.
Age and HRV in Children

As the child ages, there is generally a decrease in respiratory sinus arrhythmia. This normal arrhythmia is related to HF power (Shannon, Carley, & Benson, 1987). Shannon and associates (1987) found that when lying down, the HF power declined linearly in their subjects, 9–28 years of age. Schwartz, Gibb, and Tran (1991) reported similar findings. In 56 healthy subjects from ages 20-81 the SDNN decreased with increasing age (p < .001). The ratio of high to low frequency was not affected by age. Yeragani, Pohl, Berger, Balon, and Srinivasan (1994) studied short-term HRV using postural changes in 4–12 vs. 21-43 year olds and found significant negative correlations between age and supine VLF, LF and HF powers, and standing HF power. Children had a significantly lower supine low frequency (0.01-0.05 Hz) (p < 0.005), supine high frequency (0.2-0.5 Hz) (p < 0.001), and standing high frequency powers (p < 0.005) compared to adults. In 1997, Massin, Maeyns, Wthofs, Ravet, and Gerard (2000) determined average ranges of HRV for infants and children, ages 3 days to 14 years. They found that HRV decreased according to the mean RR interval for the length of the analysis and according to the age of the subjects (N = 210). A progressive and significant decrease of HR and increase of SDANN with increasing age was also found by Silvetti, Drago, and Ragonese (2001). Galeev and associates (2002) studied the age-related features of heart rate variability in children (N = 5400) aged of 6 to 16 years. These researchers found that SDNN and HF increase with age, changing in a “wavelike way” from year to year.

Gender and HRV in Children

Autonomic responses to orthostatic challenges are affected by gender adults studied the heart rate variability in 41 adolescents (20 boys and 21 girls) aged 12-17 years. The HRV components included; LF, HF and the LF/HF ratio. There was no significant difference in gender groups, suggesting that cardiac autonomic responses are not affected by gender in youth. Galeev and associates (2002) found gender differences between childhood and adolescence. Dividing a group of 6-16 year olds (N = 5400), these researchers observed gender differences began at the age of 11 years (LF), 12 years (HF, SDNN) and no difference in all components of HRV in 16 year old boys and girls. Though there were fewer males included in their study of African-American youth, a gender effect was reported with males (n = 26) having higher values than females (n = 49). These lower values however may have resulted from a difference in physical activity, or BMI. The LF /HF ratio in a cohort of African American and Caucasian adolescents differed significantly by gender (p < 0.01), with female subjects showing a lower value.

Gender differences are also observed. In evaluating HRV in healthy children (ages 1-5, 6-10, 11-15, 16-20 years) with 24-h ambulatory Holter monitoring, Silvetti et al. (2001) found that males showed SDNN values significantly higher than in females. Galeev et al (2002) observed gender differences in mean values of N-N interval beginning at age of 9. But for LF, the differences were observed beginning from the age of 11 and in SDNN, the differences were observed from the age of 12 years. No
differences between 16-year-old boys and girls were noted. They also recommend that their obtained values of the parameters be used in practice as reference standard.

Faulkner, Hathaway, and Tolley (2003) evaluated healthy adolescents to determine the effects of age, sex, race, BMI, and Tanner stage on HRV. They found that there was a significantly lower HRV measures for girls and African-American youth (p < 0.05) and a small correlation between Tanner stage and SDNN.

Ethnicity and HRV in Children

Research on racial differences in HRV between African Americans and Caucasian Americans is scanty and ambiguous at best, but deleterious impact of obesity seems to be greater in African Americans than in Caucasians (Gutin, Howe et al., 2005). In an adult study, Liao and colleagues (1995) reported in the Atherosclerosis Risks in Communities (ARIC) study that African Americans had a lower LF and higher HF than Caucasian Americans. A report on the effects of age and race on HRV and hypertension in a study that included African and Caucasian Americans 23-54 years of age (Choi et al., 2006; Okosun, Prewitt, Liao, & Cooper, 1999) found that young African American males manifested a pattern of HRV similar to older Caucasian Americans. But the African American males in this study were also more hypertensive. In younger African American males (mean age 21.6 years for African Americans, 23.9 years for non-African Americans). Zion et al. (2003) found that African Americans had lower HF power and higher LF/HF ratios than non-African Americans.

Though there are fewer studies in children, HRV findings may be related to race. In a smaller study of the Bogulasa Heart Study (Urbina et al., 1998), adolescent boys (n = 39), showed increased sympathetic tone in healthy white males and greater parasympathetic activity in black males. Interestingly, there was a tendency toward sympathetic control in the LF/HF ratio during testing in all of the subjects with higher of DBP, and those tended to be African American. However, there was no statistical significance. Parasympathetic activity was higher in the African-American subjects. In adults, increased sympathetic tone has been found in hypertensive individuals. And in a smaller study, of adolescent males (n = 39) higher sympathetic tone was evident during evoked maneuvers including Valsalva, isometric hand grip, and cold stress in Caucasian American versus African-American youth (Urbina et al.). In yet another study investigating the difference in HRV in young African Americans and Caucasian Americans, Wang, Thayer, Treiber, and Snieder (2005) found HRV differed by ethnic group. African American adolescents had a lower LF /HF ratio (0.09 vs. 0.33, p < 0.01), and lower HF (0.26 vs. 0.66, p = 0.047) after adjusting for age. Further, they did not find any significant effect of BMI or blood pressure on any time- and frequency-domain indexes of HRV. In the largest study to date, Faulkner and associates (2003) demonstrated lower values of 24-hour HRV measures in African-American adolescents (p <.05) compared to Caucasian Americans and indices for normal ranges of both the short-term evoked and 24-hour HRV measures were computed with 95% confidence.
intervals. These are used as a reference guide when interpreting the present study’s HRV values.

Physical Activity and HRV in Children

Research has shown that increased physical activity is associated with higher levels of overall autonomic nervous system activity in adults (Amano, Kanda, Ue, & Moritani, 2001; Davy, DeSouza, Jones, & Seals, 1998; Davy, Tanaka, Andros, Gerber, & Seals, 1998; Goldsmith, Bigger, Steinman, & Fleiss, 1992) and obese children (Davy, Harrell, Stewart, & King, 2004; Gutin, et al., 1997).

Effective Programs for Weight Management

Programs for weight control in youth may include diet, behavioral modification, lifestyle, exercise, medications and surgery. Some will have parental involvement and some will attempt to influence children without parental input. The ADA (2006) advises there be a combination of school and home intervention. The American Academy of Pediatrics best advice is prevention and teaching of good nutrition but what was once considered sound advice of reducing fat in the diet may not be the answer (Ebbeling, Leidig, Sinclair, Hangen, & Ludwig, 2003; Whitlock, Williams, Gold, Smith, & Shipman, 2005). The results of weight loss programs in youth, regardless of their content, have been mixed with no clear cut method of genuine effectiveness. Murtaugh, Dixey, and Rudolf (2006) interviewed 20 overweight boys age 8-14 years individually and in a group, in an effort to ascertain what barriers effectiveness. The researchers reported that sacrificing in terms of giving up certain foods was problematic. Shapedown uses a self directed format to encourage small changes (Mellin, Slinkard, & Irwin, 1987) that are more palatable and therefore sustainable. The children also reveal a communication disconnection between patient and provider and parental tolerance or lack of awareness of the child’s obesity. Murtaugh and others (2006) also described that compliance could be improved with continuous and developmentally appropriate encouragement.

No differences in percentage of body fat or visceral adipose tissue were detected between the groups when Gutin, Cucuzzo, Islam, Smith, and Stachura (1996) compared lifestyle education only with lifestyle education plus moderate or high-intensity physical activity. However, in a meta-analysis of weight management programs for youth, (Snethen, Broome, & Cashin, 2006) found limited effective interventions. Weintraub et al. (2008) implemented a six-month after school sports program for 4th and 5th graders (N = 21) at above the 85th % percentile for BMI. The children were randomized to a soccer team (N = 9) or a health education group. All 9 children in the soccer group plus health education and 5 of 12 children (42%) in the health education only group had lower BMI z scores at 3 and 6 months. The children and parents were so enthusiastic about playing, they asked for expansion of the program in the last month of the study. The success of this program may be attributed to the restriction of participants to overweight children only and the enthusiastic participation of parents. Using behavior modification that includes parent activities, Savoye et al. (2007) documented six-month improvements
children that were sustained at 12 months in weight management vs. control, including changes in the following: weight (+0.3 kg [–1.4 to 2.0] vs. +7.7 kg [5.3 to 10.0]); BMI (–1.7 [–2.3 to –1.1] vs. +1.6 [0.8 to 2.3]); and body fat (–3.7 kg [–5.4 to –2.1] vs. +5.5 kg [3.2 to 7.8]). Because the weight change data is not reported in the same manner it is not possible to compare the amount of weight loss, but perhaps the commonality, caregiver involvement is the key.

There are no studies found that evaluate behavior modification alone, but there were many that investigated some variation of behavior, diet and physical activity. To evaluate the effects of the weight management program Bright Bodies, Savoye and associates (2007) compared a family-based program including exercise, nutrition, and behavior modification to a control group who received traditional weight counseling every 6 months. The test group underwent behavior modification was in the form of workbook designed specifically for obese children. The caregivers were given classes that related to the problems expressed by parents during the study. The exercise portion of the intervention was 50 minutes twice a week, with encouragement to exercise 3 days a week at home. The structured diet segment of the program was suspended because of the high drop out rate. Savoye and associates (2007) documented six-month improvements that were sustained at 12 months in weight management vs. control, including changes in the following: weight (+0.3 kg [–1.4 to 2.0] vs. +7.7 kg [5.3 to 10.0]); BMI (–1.7 [–2.3 to –1.1] vs. +1.6 [0.8 to 2.3]); and body fat (–3.7 kg [–5.4 to –2.1] vs. +5.5 kg [3.2 to 7.8]). With this intervention, the researchers showed that combining simple routine obesity education and counseling regarding the concerns of the parents with moderate regular exercise has a positive effect on the metabolic risks of children. Harden and associates (2007) reported weight loss in a group of adolescents using lifestyle interventions, and though they cohort lost weight, but those who also used metformin had the better outcome. However, the metformin group consisted of fewer African Americans, but those who were more severely obese (measured by weight, BMI, and RBMI), and greater number of youth with diabetes.

**Diet Component**

Some researchers are looking at not only total calorie intake, but the types of calories consumed for a clue to weight loss effectiveness. Ebbeling and colleagues (2003) compared reduced fat intake to low to moderate glycemic index in obese adolescents aged 13 to 21 years. At 12 months BMI and fat mass had decreased more in those who decreased their glycemic index intake vs. a decrease in fat intake. However, the total number of calories consumed was not reported for either group. Spieth and colleagues (2000) found similar results in another study comparing a reduced-glycemic-load diet with a conventional reduced-fat diet in adolescents in an intensive 6-month educational and behavioral weight-control program. At 12 months, mean BMI decreased in the reduced-glycemic-load diet group (–1.2 ± 0.7 kg/m²) and increased in the reduced-fat diet group (0.6 ± 0.5 kg/m²; P < .02). However, Figueroa-Colon, Franklin, Lee, von Almen, and Suskind (1996) accessed protein sparing calorie restricted diet in “super obese” pre-adolescent children. At the 6-month mark, 50% of the children were no longer classified
as super obese. The results of these diet changes perhaps does not depend on the type of diet, but perhaps the reduction of total calories consumed. In the Shapedown program (Mellin et al., 1987), very low calorie or restrictive diets are discouraged, and information for youth and parents regarding small manageable diet changes are taught by nutritionists.

**Physical Activity Component**

Physical activity improves muscle strength and endurance, decreases blood pressure and resting heart rate and helps in weight maintenance. In more recent studies physical activity is associated with improvements in insulin sensitivity, inflammatory and thrombotic markers and heart rate variability. High levels of physical activity were significantly and positively associated with insulin sensitivity in adolescent boys but not girls (Imperatore, Cheng, Williams, Fulton, & Gregg, 2006). However, in this same study, an inverse relationship with physical activity and BMI was evident in girls. Imperatore and associates (2006) suggest the purpose of physical activity in girls is weight maintenance. There may be some evidence that supports this notion. Nassis, Psarra, and Sidossis (2005) conducted a 12-week exercise program with only overweight and obese girls. They too found no weight loss associated with physical activity, but unlike Imperatore and associates, they found that insulin sensitivity was improved. In boys vs. girls, a group of overweight and obese African-Americans adolescents, the boys spent significantly more time being physically active and had more vigorous activity, but there was not a significant difference in insulin sensitivity (Snitker, Le, Hager, Caballero, & Black, 2007). Insulin resistance improved in a mixed age, race and sex group of children who participated in a yearlong weight management program (Savoye et al., 2007), but the improvement in IR could also be related to weight loss.

Inactivity is directly related with obesity. Salbe and colleagues (2002) found in a cohort of 5-year-old Pima Indians that weight was positively correlated with television watching and negatively correlated with physical activity. Marshall, Biddle, Gorely, Cameron, and Murdey (2004) found a similar relationship between TV viewing and body fatness among children and youth 3 to 18 years old and a negative relationship between TV viewing and physical activity. Giugliano and Melo (2004) found weight was directly correlated with daily sitting hours in 452 school children.

In a cohort of 25 obese children, a correlation was found between an inflammatory marker (CRP) and fasting insulin \( (r = 0.62; P < .001) \). The subjects VO2 peak, brachial artery flow-mediated dilation (FMD), lipids, oral glucose tolerance, body composition, aerobic fitness at peak oxygen uptake (VO2 peak), and blood pressure were also measured. After 8 weeks, there was no significant change in obesity measure, but significant improvements in VO2peak, HDL cholesterol, and FMD were seen in the group assigned to aerobic exercise.

The intensity of exercise may affect HRV and fitness. To correlate the response of VO2max, HR, HRV [HF/(LF+HF)] with intensity of physical activity, Buchheit, Platat,
Oujaa, and Simon (2007) studied 67 12-year-old preadolescents. Physical activity was evaluated by triaxial accelerometry. The youth were classified as usually participating or not participating in moderately intense activity (> 4 METs) for 210 minutes per week [4 M (210)], and usually participating or not participating in intense activity (> 6 METs) for at least 60 min per week [6M (60)]. Moderately intense activity [4 M (210)], and higher intensity [6 M (60)] were associated with higher VO2max but only 6M (60) was associated with improved HRV measures. This may suggests that more intense activities are necessary to benefit cardiac autonomic measures. Fitness levels have shown a negative relationship with inflammation. In a large group of 10-15 year olds, unfit children exhibited systemic inflammation but obese children who were none the less fit had CRP levels comparable to lean and fit children (Halle, Korsten-Reck, Wolfarth, & Berg, 2004).

To evaluate the feasibility, acceptability, and efficacy of an after-school team sports program for reducing weight gain in low-income overweight children, Weintraub and associates (2008) implemented a 6-month after school sports program for 4th and 5th graders (N = 21). The children were randomized to a soccer team (N = 9) or a health education group. All participants were at above the 85th % percentile for BMI. All 9 children randomized to the soccer group and 5 of 12 children (42%) randomized to the health education group had lower BMI z scores at 3 and 6 months. What is also interesting to note is that the children and parents were so enthusiastic about playing, they asked for the program to expand from 3 days a week to 4 days a week for the last month.

Gutin and associates (2002) compared lifestyle education only with lifestyle education plus moderate or high-intensity physical activity. No differences were seen between the groups in their percentage of body fat or visceral adipose tissue.

Conclusion

Reduced physical activity and increased sedentary behaviors is possibly the root of childhood obesity (Gortmaker et al., 1996; Reilly & Dorosty, 1999; Troiano & Flegal, 1998), as activity negatively correlates with obesity (Gregory, Martorell, Venkata-Narayan, Ramirez-Zea, & Stein, 2009; Troiano & Flegal). Obesity is a very difficult disorder to treat and the pediatric age group can be an especially difficult population as they are somewhat confined by the will and the authority of others. Although treatment goals for overweight children are similar to those recommended for adults (dietary modification and physical activity), weight loss per se is not necessarily the best strategy (Daniels, 2005). Treatment modalities for children present a unique challenge as nutrition education, physical activity, and behavior modification must be presented to both the caregiver and child, with the caregiver being the major agent of change in the family (Golan & Crow, 2004). Treatment strategies for childhood and adolescent obesity should be multidisciplinary, supportive, and ongoing. Parents should play an integral role in supporting the treatment process and being active role models with respect to eating behaviors and physical activity. The intervention used in this study, SHAPEDOWN is a weight intervention developed for adolescents in 1977 at the University of California,
Effect of Weight Loss on Fitness, HRV, and the Components of the Metabolic Syndrome

Obesity and lack of exercise tend to lead to IR (Froberg & Andersen, 2005). Insulin resistance has a negative effect on lipid production, increasing VLDL, LDL, and triglyceride levels and decreasing HDL (Howard, 1999). This can lead to atherosclerosis and over time can lead to cardiovascular heart disease, thrombosis, and cerebral vascular accidents. Insulin resistance also leads to increased insulin and glucose levels in the blood. Excess insulin increases sodium retention by the kidneys, which increases blood pressure and can lead to hypertension (Krauss, Winston, Fletcher, & Grundy, 1998). Chronically elevated glucose levels in turn damage blood vessels and organs, such as the kidneys, and may lead to diabetes. Andersen and colleagues (2006), tested 915 girls and 817 boys (9 and 15 year olds) for risk factors associated with the Metabolic Syndrome to determine relationships among physical activity (PA) and clustering of cardiovascular disease risk factors. The authors reported weak associations between PA and all risk factors; the strongest association was with physical activity and insulin. They further reported there was a dose response relationship between physical activity and all risk factors.

Savoye and associates (2007) found positive change in components of the Metabolic Syndrome in a study of a weight management program for obese children (BMI > 95% percentile for age and sex) age 8-16 year. The biomarkers of the Metabolic Syndrome were positively affected with weight loss were HOMA-IR (−1.52 [−1.93 to −1.01] vs. +0.90 [−0.07 to 2.05]) and fasting insulin (−6.1 [−8.1 to 4.0] vs. +4.5 [−0.2 to 9.6]). Figueroa-Colon and colleagues (1996) found a decrease in blood pressure and lipids after 6 months of weight loss in obese children, and is further illustrated in a 3 week weight loss program (Sudi et al., 2001). Though the weight loss was small (mean = -3.76kg ± 1.22) in these children, changes in insulin (r = 0.15 p = 0.0015) and triglycerides (r = 0.587, P < .0001) was noted. However, the study also enlisted physical training; walking, brisk jogging, biking, and playing different ball games 3 times per day, lasting approximately 1.5 hours which could significantly affect insulin and triglyceride levels.

There is little research found on the effect of weight loss on HRV in children. In an obese adult population that experienced weight loss and bariatric surgery, Nault and associates (2007) demonstrated improvement in SDNN (116 ± 25 vs. 174 ± 56 ms, p < .001). Holter monitoring results demonstrated a decrease in minimal heart rate (48 ± 10 vs. 40 ± 6 beats per minute, p = .021) and mean heart rate (82 ± 7 vs. 66 ± 10 beats per minute, p < .001). Another group (Poirier, Hernandez, Weil, Shepard, & Eckel, 2003)
showed an increase in parasympathetic tone after a 10% weight loss from a 3 month calorie restricted diet. However, there was no significant change in insulin, glucose, blood pressure or total cholesterol. In a 3 week intensive intervention for obese adults that included strict calorie intake and intense exercise (Facchini et al., 2003), average BMI was reduced from 41.4 to 39.5 kg/m², and average heart rate from 77.8 to 73.6 b/min. Significant changes in the HRV measures were also noted as evidenced by +31.8%; low frequency oscillation, LF: +17.1%; high frequency oscillation, HF: ± 18.2%. These results, demonstrate that a small weight reductions improved HRV. 

However, most studies regarding cardiac autonomic changes after weight loss do not discern acute or continuing weight loss and weight maintenance. Laaksonen, Laitinen, Schonberg, Rissanen, and Niskanen (2003) studied men and women who underwent a 9-week weight loss program and sustained that weight loss for a year. Though there was a decrease in insulin, blood pressure, and an increase in LF at 9 weeks, blood pressures trended toward their pre-weight loss levels and LF increased by 46% by the end of the study. Insulin rose but was still significantly decreased at year’s end.

**Conclusion**

Metabolic Syndrome is a set of risk factors that includes: a decreased ability to process glucose, obesity, dyslipidemia, and hypertension. There are five major definitions for Metabolic Syndrome in adults (Strazzullo et al., 2008). The differences in definitions create difficulties when comparing results across studies but it also provokes difficulty in defining the syndrome in youth. In fact, one meta-analysis found 46 different definitions of the syndrome pertaining to children (Ford & Li, 2008). To increase the confusion, there is no consensus regarding the values or cut-points for each of the included components. Most likely because of these differences, the overall prevalence estimates of the Metabolic Syndrome in children range from 4.2% to 50.0%.

The American Heart Association has identified the major cardio-vascular disease risk factors as obesity, hyperinsulinemia, dyslipidemia and hypertension (Grundy, Pasternak, Greenland, Smith, & Fuster, 1999). And individuals with multiple risk factors are at a higher risk of developing CVD and T2DM. Also seen with Metabolic Syndrome but not included with the criteria are proinflammatory tendencies. A correlation was found between inflammatory markers and the Metabolic Syndrome components and studies suggest propose these markers increase the risk for CVD and T2DM (Rader, 2000).

Heart rate variability is an important quantitative marker of cardiovascular regulation by the autonomic nervous system. Loss of heart rate variability is an independent predictor of mortality after an acute myocardial infarction (Bigger, et al., 1994; Kitney & Rompelman, 1980; Kleiger, et al., 1987; Malik, et al., 1989), is indicative of ventricular dysfunction in patients with congestive heart failure (Bilchick et al., 2002; Ponikowski et al., 1997). In children and adolescents, the measures of HRV have had limited study and thus normative values are still elusive. Although the mechanisms are
not fully understood, the markers of the Metabolic Syndrome are interrelated and inflammation and fitness may be pathways to effect on all components.
CHAPTER 3: METHODOLOGY

This chapter provides a detailed description of the study design, sample, setting, and the instruments. Procedures for data collection and statistical analyses, as well as protection of human subjects, are discussed.

Design

The study employed a correlational design with post-hoc analysis of pre and post-intervention data obtained from youth who participated in two arms of a weight loss, intervention program at the Youth Lifestyle Clinic at LeBonheur Medical Center. This secondary data analysis examined the prevalence of the metabolic syndrome in this group of overweight adolescents and explored relationships among HRV, fitness, inflammation, and components of the metabolic syndrome. Post-hoc analysis of the effect of weight loss (change in obesity severity) on components of the metabolic syndrome and heart rate variability were examined.

Sample and Setting

De-identified data were obtained from records of youth enrolled in a weight loss, intervention study from March 2002 through March 2004. The initial study consisted of a convenience sample of 50 African-American subjects recruited from the Youth Lifestyle Clinic at LeBonheur Medical Center, the only referral clinic for overweight youth in the Greater Memphis area within a 200-mile radius. Study measures were conducted at the Center for Health Evaluation and Lifestyle Promotion (HELP Center), a research and practice site of the College of Nursing at the University of Tennessee Health Science Center. The weight loss intervention was conducted at the Youth Lifestyle Clinic. For the purpose of the current study, all subjects with data sets on the variables of interest at baseline (n = 50); and all subjects with both pre and 6-month post intervention data (n = 39) were included in this secondary data analysis. Detailed characteristics of the study participants are provided in Chapter 4.

Inclusion Criteria

Eligibility requirements for the original study included male and female African-American youth between 7-18 years of age who were overweight or obese (BMI ≥ 85th percentile based on age and gender specific growth charts). Subjects and parents had the ability to read and write English and were willing to participate in a longitudinal weight loss study.
Exclusion Criteria

Youth were excluded from study participation if they met the following criteria:

- Physical limitations that impaired their ability to complete the exercise test (treadmill)
- Previous diagnosis of diabetes
- Current medication therapy that affects body weight, glucose or lipid metabolism including estrogen contraceptives or anticoagulants
- Pregnancy
- Documented cardiac defect
- Cognitive impairment (more than 2 grades behind age appropriate grade in school)
- Weight > 350 lbs (upper limit for equipment, DEXA and treadmill)

Intervention: Standard Care versus Shapedown Program

Youth were randomized into one of two weight loss programs: standard clinic care or Shapedown. Children in both intervention groups underwent evaluations of body composition, growth and development, dietary and activity practices, and psychosocial needs. Group counseling regarding the effect of obesity on health and nutritional and physical activity strategies for weight loss were provided to both the standard care and Shapedown groups. Subjects in the standard clinic care group was seen individually, with their parents, every month by the multidisciplinary team (physician, nurse, educator, nutritionist, and social worker) and underwent evaluation of weight loss, growth and development, dietary and activity practices, and psychosocial needs with individualized education on lifestyle modifications provided.

In addition to routine clinic care, subjects randomized to the Shapedown program, and their parents, received weekly group support and educational sessions for 6 months. Shapedown was first developed in 1979 at the School of Medicine, University of California, San Francisco with support from federal and health agencies. The program employs a variety of cognitive, behavioral, and affective techniques adapted to make successive small modifications in diet, exercise, communication, and affect that are sustainable. Parents were instructed on strategies for supporting their children’s weight-loss efforts.

For the purpose of the current study, the data from all subjects, regardless of the weight loss program they participated in, were included. This investigation examined the prevalence of metabolic syndrome components in obese African-American youth and explored relationships among the presence of Metabolic Syndrome components, fitness, heart rate variability, and inflammation regardless of the type of weight loss program. Additionally, predictors of weight loss (age, gender, baseline fitness) were explored and the relationship between changes in obesity, fitness, and heart rate variability were examined. Because both intervention groups received non-pharmacological interventions
with similar content on lifestyle modifications (diet and physical activity), it was deemed appropriate to include subjects from both intervention arms.

**Recruitment**

For the original study, youth and their parents were informed of the study by one of the investigators during their initial visit to the Youth Lifestyle Clinic. If they were interested in receiving further information regarding the study, the investigator met with them to explain the study and provide opportunity for questions. Additionally, youth and their parents were given the opportunity to ask questions of the investigator without the other being present, and to verbally consent to study participation without coercion from family members. Youth who agreed to participate in the study provided written assent and a parent or legally authorized representative provided written informed consent. To facilitate subject participation, weekend scheduling was available and reminder calls and mailings were done to minimize missed appointments.

For the current study, Institutional Review Board approval was obtained to conduct a secondary data analysis of existing de-identified data. Individuals who participated in the study were not recontacted and no additional data was solicited.

**Instrumentation and Procedures**

As part of the initial data collection process, subjects underwent a physical examination with measurement of resting blood pressure, anthropometric measures, a mixed meal tolerance test to assess glucose metabolism, and phlebotomy for cardiac and metabolic risk markers. The investigator conducted a 24-hr diet diary recall interview (Johnson, Hackett, Roundfield, & Coufopoulos, 2001) and 7-day Physical Activity Recall (Sallis, Buono, Roby, Micale, & Nelson, 1993) with subjects. Additionally, subjects completed a carbohydrate craving questionnaire and the Childhood Depression Inventory (Kovacs, 1981). Tanner staging was performed by the researcher, if not previously performed at the time for study recruitment. A maximal cardiopulmonary treadmill fitness test was conducted and following a 15-minute rest period, a 24-hour Holter monitor was placed for acquisition of HRV data. Subjects were randomized to either the Shapedown or standard clinic, weight loss intervention and retested 6 and 12 months later using the same study instruments. Parents completed an investigator-developed demographic questionnaire on themselves and their child.

The current study involved a secondary data analysis of data collected from the blood pressure and anthropometric measures, the mixed meal tolerance test, blood work, the fitness testing, and HRV analysis of the 24-hour Holter monitor at baseline and 6 months post-intervention. The age and gender of the youth were obtained from the demographic questionnaire. The following sections describe each instrument used in the current study and the procedures associated with data acquisition in the original study associated with those instruments.
Instrumentation

**Demographic Data.** An investigator-developed questionnaire was used to ascertain parental and child demographic information and lifestyle behaviors. Questionnaires were completed at the time of study consent or at the first study visit. For the current study, the child’s age (in months) and gender were used to describe the study sample and accurately determine percentile placement on age and gender normative charts.

**Anthropometric Measures.** Body mass index is recommended as the preferred methods for determining obesity as it correlates well with body fat in adults (Bertakis & Azari, 2005) and children (Freedman, et al., 2006; Harden, et al., 2007; Velasquez-Mieyer, Neira, Nieto, & Cowan, 2007). At each study visit, the subject’s body weight was measured to the nearest 0.1kg with a calibrated electronic scale (Detecto, Webb City, MO) which has an accuracy of ± 0.02kg. Height was measured to the nearest 0.1 cm with a stadiometer (Holtain Ltd, Croswell, Crymych, United Kingdom). BMI was calculated as weight in kilograms divided by height in meters squared (kg/m^2). Overweight and obesity are defined as a BMI ≥ 85th and BMI ≥ 95th percentile on CDC BMI charts (CDC Growth Charts, 2000). These BMI cut-offs points are linked to adult cut-off points for overweight and obesity, which are good indicators of risks for adverse health outcomes (Cervenakova, Ksinantova, & Koska, 2002). Relative BMI (RBMI) was used as an estimate of the percent overweight and used to track weight loss progress over time. RBMI was calculated using the following equation: actual BMI divided by the 50th percentile BMI on CDC chart for gender and age, then multiplied by 100 (Velasquez-Mieyer et al., 2003).

Waist circumference was measured while the subject was standing, using a metal tape measure at just above the uppermost lateral border of the right ilium, at the end of a normal expiration, and was recorded at the nearest millimeter, as described by the National Center of Health Statistics. For the current study, visceral adipose tissue was categorized using waist circumference cut-points as described by Fernandez et al. (2004) according to the youths’ age and race. These waist circumference percentiles were derived from a nationally representative sample of African-American, European-American, and Mexican-American children and adolescents (Fernandez et al., 2004). All anthropometric measures were performed by the same researcher.

**Laboratory Measures.** After a 10-hour overnight fast, an intravenous catheter was placed in the antecubital area of the child’s arm, and fasting and two hour post-glucose load blood samples were obtained. Blood samples were sent to LINCO (St. Louis, MO) for assessment of glucose and insulin levels, while measurement of lipid levels and inflammation markers completed as part of the routine clinical care.

**Lipid Profile.** Serum HDL-cholesterol and triglycerides were measured using an automated analyzer (Roche Cobas-Mira) utilizing the manufacturers commercially...
available kits. Values were expressed as mg/dL. Study values are compared to normative values derived from data collected during the National Health and Nutrition Examination Surveys (Hickman, et al., 1998). These data were used to develop age- and gender-specific thresholds that denote abnormal levels of total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides. This classification system takes into account gender differences or the natural fluctuations in lipoprotein concentrations that occur with growth and maturation. Normal lipid values for children were defined according to percentile cut points within population distributions. The cut points of > 90th% percentile was used for triglycerides and < 10th % percentile for HDL cholesterol was used as criteria measures for the metabolic syndrome in this study.

**Inflammation Marker.** Fibrinogen (mg/dl) and C-reactive protein levels (mg/L) were measured. Fibrinogen levels were measured using modified thrombin time with photo-optical measurement of turbidity. C-reactive protein levels (mg/L) were assessed using Dade-Behring nephelometer with the manufacturer’s reagents, quality controls and methods. Fibrinogen values between 200 mg/dl and 400 mg/dl were considered normal based on reference values provided LabCorp and Quest Diagnostics, while CRP values > 1 mg/L were considered elevated.

**Glucose and Insulin Indices.** A 2-hour mixed meal tolerance test (MMTT) was performed. The subject drank 240 ml of Boost, ingesting all within 5 minutes, and blood samples were obtained at 0 and 120 minutes for glucose and insulin levels. Boost contains 1.01kcal/ml with the following nutritional content: protein 17%, carbohydrate 67% and fat 16%. IV access was maintained by flushing every 30 minutes with 5cc of normal saline. Use of heparin was contraindicated as it increases non-esterified free fatty acid levels and may influence the insulin dynamics. Serum glucose was measured by the glucose oxidase method (Kadish, Little, & Sternberg, 1965). Insulin (µU/ml) was measured by standard double-antibody radioimmunoassay (RIA) (Linco Research; St. Louis, MO). Insulin and glucose levels were used to calculate QUICKI, a measure of insulin resistance, using the following formula: \[ \text{QUICKI} = 1 / \left[ \log \text{plasma fasting insulin (mU/l)} + \log \text{plasma fasting glucose (mg/dl)} \right] \]. The correlation between QUICKI and measures of insulin resistance derived from glucose clamp studies, the gold standard assessment insulin resistance, was comparable to that between homeostasis model of assessment and Siclamp \( r = 0.82 \) (Chen et al., 2003). QUICKI values < 0.3 have been shown to predict impaired glucose tolerance in overweight youth (Velasquez-Mieyer et al., 2008). Insulin resistance was defined as a QUICKI value < 0.3.

The 2009 ADA diagnostic guidelines were used to distinguish normal verses impaired glucose tolerance (IGT). The ADA (2009) acknowledged a group of subjects whose glucose levels are too high to be considered normal but do not meet the criteria for diabetes. Table 3.1 depicts fasting and two-hour glucose levels for the categories of normal glucose tolerance, impaired glucose tolerance, and diabetes. There are no differences in cut-points for children and adults.

Table 3.1
Table 3.1. Categories of Glucose Metabolism

<table>
<thead>
<tr>
<th>Categories</th>
<th>Fasting Plasma Glucose</th>
<th>Plasma Glucose 2-Hour Post Glucose Load</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal glucose tolerance</td>
<td>&lt; 100 mg/dl</td>
<td>&lt; 140 mg/dl</td>
</tr>
<tr>
<td>Impaired glucose tolerance</td>
<td>&gt; 100 mg/dl but &lt; 126 mg/dl</td>
<td>&gt; 140 mg/dl but &lt; 200 mg/dl</td>
</tr>
<tr>
<td>Diabetes</td>
<td>≥ 126 mg/dl</td>
<td>≥ 200 mg/dl</td>
</tr>
</tbody>
</table>
**Resting Blood Pressure.** After the MMTT was complete, the child rested in a sitting position for 15 minutes and resting BP was measured. BP measurements were obtained by the same researcher using techniques recommended by the Task Force on High Blood Pressure in Children and Adolescents. The investigator obtained two BP readings, 5-minutes apart, with an appropriate sized cuff while the subject was in a sitting position. The current study used blood pressure parameters as defined by the National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents (Falkner & Daniels, 2004) to classify subjects’ blood pressure readings (age, sex, and height).

- Systolic and diastolic BP < 90th percentile is normal.
- Either systolic or diastolic BP between the 90th and 95th percentile is prehypertension.
- In adolescents, 12 years of age or older, BP ≥ 120/80 mmHg is prehypertension, even if this figure is < 90th percentile.
- Systolic or diastolic BP > 95th percentile may be hypertension.

**Metabolic Syndrome.** Although Metabolic Syndrome is a well-recognized clinical phenomenon, there is no internationally accepted definition in childhood. For the current study, subjects were classified as having the Metabolic Syndrome based on criteria proposed by WHO (2004). This definition of the Metabolic Syndrome required the presence of insulin resistance, impaired glucose tolerance or T2DM plus 2 of the remaining risk factors. The other four risk factors include central adiposity, high systolic blood pressure, high triglycerides, and low HDL-C. The prevalence of the various Metabolic Syndrome components were determined based on the measurement cut-points detailed in Table 1.1.

**Cardiorespiratory Fitness.** Multistage treadmill exercise protocols are suitable for assessing cardiorespiratory fitness in obese youth (Owens & Gutin, 1999). Oxygen consumption at maximal exercise (VO2max) is the “gold standard” for measuring cardiorespiratory fitness and reflects the ability of the cardiopulmonary system to deliver oxygen to working muscles, as well as the ability of the muscles to use oxygen efficiently (American College of Sports Medicine [ACSM], 2005). In the original study, a cardiopulmonary maximal treadmill graded exercise test was conducted using the Branching Protocol. Measurement of oxygen consumption at maximal exercise (VO2max) was assessed using the Sensor-Medics Vmax V6200 metabolic cart. Volumetric and gas calibrations were done prior to each testing session.

Prior to initiating fitness testing, subjects received instruction on how to walk on the treadmill and rate their perceived exertion. The anterior chest of each subject was cleansed with sterile rubbing alcohol and hair shaved, if necessary, to assure adequate electrode contact with the skin. A standard 12-lead electrocardiogram placement was performed. Resting and standing 12-lead EKGs with concomitant blood pressure measurement using an upright mercury sphygmomanometer were obtained prior to starting the fitness test to ascertain any contraindications to fitness testing and provide a baseline comparison. Throughout the treadmill fitness test, there was continuous EKG monitoring.
and BP was taken during each 2-minute stage using a stethoscope and sphygmomanometer. The Borg Rating of Perceived Exertion Scale was used to ascertain the subject’s level of exertion during each stage of the fitness test.

Subjects were fitted with a clean mouthpiece, which was held in place with a head support, and a nose clip was applied. Collection tubing was attached to the Sensor-Medics Vmax V6200 metabolic cart for continuous measurement of oxygen consumption (VO₂) and metabolic measures.

Subjects straddled the treadmill with both legs while the treadmill was turned on at a speed of 1.5 mph and 0% incline. During the 2-minute warm-up phase, the investigator coached the subject to assure the mouth remained firmly closed around the mouthpiece and resting on the support bars did not occur. Thereafter, the treadmill speed was advanced every 2 minutes until a brisk walking speed of 3.0 or 3.5 mph was reached, after which the treadmill speed was maintained and the incline was raised every 2 minutes to increase the work intensity equivalent to 1 MET for each stage, until the subject reached volitional fatigue or exhibited criteria for exercise cessation. Those criteria include an abnormal BP response (SBP > 240 mmHg or DBP > 120 mmHg or a fall in SBP > 20 mmHg), arrhythmias, ST segment changes, lightheadedness, nausea, cyanosis, angina or excessive dyspnea (ACSM, 2005). A passive recovery followed with continuous EKG monitoring and BP taken every 2 minutes until values returned to baseline. For the current study, VO₂max, expressed in mg/kg/minute, was used as the measure of cardiorespiratory fitness.

24-Hour Heart Rate Variability Measures. Heart rate variability is the term used to describe variations of both instantaneous heart rate and RR intervals. After resting for 15 minutes, EKG patches were applied to achieve EKG readings using a lead I and modified V1 chest lead on the Series 8500 24-hour Holter monitors. Subjects were instructed to engage in normal daily activities during the data collection period with the exception of any activities that would subject the monitor to water. A diary was provided to subjects for documentation of sleep, exercise, illness, and unusual stress. At the conclusion of the 24-hour period, subjects or their parents removed the Holter monitor and returned it to the HELP Center for analysis. EKG tapes were submitted to the Marquette Electronics Laser SXPR Ambulatory ECG Analysis and Editing Systems, version 5.8 software program (Marquette Electronics, Milwaukee, WI) for analysis of heart rate variability. Each QRS complex was digitized, identified, and labeled. The analyzed data file was then scanned and manually edited to locate and correct any errors in QRS labeling that would adversely affect measurement of heart rate variability and therefore internal validity (Fleiss, Bigger, & Rolnitzky, 1992). All tapes had at least 18 hours of analyzable data. Using this data file, 24-hour heart rate variability with power spectral analysis was calculated and express as the log milliseconds squared [ln(ms²)]. Kleiger et al. (1987) reported data on reliability attesting to the reproducibility of 24-hour HRV measurements.

Time domain analysis is computed on altered versions of the measurement of the standard deviation of heart period on the basis of sinus R-R intervals over time (Cowan,
That is, the intervals between successive normal QRS complexes are determined in a 24 hour Holter. After each QRS complex is detected, the normal-to-normal (NN) intervals (that is, all intervals between adjacent QRS complexes resulting from sinus node depolarizations) are determined. Simple time domain variables that can be calculated include the mean NN interval, the mean heart rate, the difference between the longest and shortest NN interval, the difference between night and day heart rate (Hayman et al., 2007). The time domain analysis examines interbeat variability directly from R-R intervals using means and standard deviations. The SDNN, which is the standard deviation of all R-R intervals during the 24-hour period, reflects circadian fluctuation and values less than 50 milliseconds are associated with sudden cardiac death (Kleiger, et al., 1987). Cowan (1995) confirmed positive correlations between frequency domain variables using two different methods of HRV analysis, Fast Fourier Transform and Autoregressive (r = .97 and r = .99). Cowan also described the validity of the time domain variable measurements showing positive correlations (r = .90) among the individual values.

Frequency domain analysis involves power spectral density (PSD) techniques that convert variances in R-R interval length into frequency waveforms. These frequency waveforms reflect parasympathetic and sympathetic neural fluctuations. The low frequency band (LF, 0.04-0.15 Hz), which estimates primarily sympathetic along with some parasympathetic modulation, and power in the high frequency band (HF, 0.15-0.40 Hertz), which represents parasympathetic modulation. The LF/HF ratio is a measure of sympathetic modulation and HF power as a measure of parasympathetic modulation. Cowan (1995) showed positive correlations of the time domain variables with the frequency domain variables.

Post-Intervention Testing

Study measures were repeated at 6 and 12 months in the same sequence as baseline measures. For this secondary data analysis, only the baseline and 6 month values were used to assess weight loss. In adults, weight loss success has been defined as either > 10% of baseline weight or 10% of excess weight. Studies in adults have shown that modest weight losses of 5-10% provide protective metabolic effects (Seidel, Powell, Zgibor, Siminerio, & Piatt, 2008). The magnitude of weight loss needed to elicit metabolic changes in obese youth has not been elucidated. For this secondary data analysis, weight loss was assessed in as the change in RBMI and calculated by subtracting RBMI at six months from the baseline value.

Data Management

The original de-identified data was stored on separate Microsoft Excel spreadsheets. For the current study, data was merged by study identification numbers into one spreadsheet. The SAS Statistical Software Package, version 9.1 (Cary, NC) was used for statistical analyses. Descriptive statistics (i.e., mean, median, mode, standard
deviation, range, frequency) were used to characterize the demographic profile of the subjects, as well as their anthropometric measures, fitness level, metabolic syndrome profile, and heart rate variability. Appropriate parametric and nonparametric correlational and inferential statistics were used to address the study aims. The level of significance was set at 0.05 for each analysis.

Statistical Analysis

Aim 1

*Describe the prevalence of Metabolic Syndrome components and the Metabolic Syndrome.* To address this aim, the components of the Metabolic Syndrome were first identified, and then evaluated as to whether or not they fell within the range of their prospective normal values. The prevalence of the components of the Metabolic Syndrome was determined by the proportion of the sample that had the risk factor divided by the total number of individuals in the sample. Subjects were classified as having the Metabolic Syndrome based on previously criteria. The prevalence of the Metabolic Syndrome was determined by the proportion of the sample that meet the criteria for the Metabolic Syndrome divided by the total number of individuals in the sample.

Aim 2

*Describe heart rate variability, fitness levels, and levels of inflammation markers.* To address this aim, descriptive analysis including mean, standard deviation, median and range were calculated at baseline.

Aim 3

*Explore relationships among the presence of Metabolic Syndrome components and fitness: oxygen consumption at maximal exercise (VO₂max), HRV (parasympathetic function and circadian rhythmicity), and inflammation (C-reactive protein and fibrinogen) at baseline.* Spearman’s rho correlation coefficients were calculated as a measure of the strength and magnitude of the relationship among the variables. Because normal values for components of the Metabolic Syndrome vary by age, correlations among raw values of Metabolic Syndrome components and other measures may be less meaningful. Thus, subjects were classified into two groups based on the presence of specific components of the Metabolic Syndrome and nonparametric t-tests (Mann-Whitney Wilcoxon) were used to evaluate potential differences in HRV, fitness, and inflammation markers between components of the Metabolic Syndrome groups. The level of significance is set at 0.05.
Aim 4

*Explore the effect of age, gender, and baseline fitness on weight loss (change in Relative Body Mass Index (RBM)).* Multiple linear regression analysis was used to determine if demographic variables of age and gender, and baseline fitness ($VO_2\text{max}$) could explain a significant proportion of the weight loss variance. Statistical significance was set at the 0.05 level.

Aim 5

*Examine the relationship among the changes in severity of obesity (change in RBMI), change in fitness ($\Delta VO_2\text{max}$), and change in HRV measures of parasympathetic function (high frequency [HF]), circadian rhythmicity (standard deviation of R-R intervals of QRS complexes of normal beats [SDNN]), and sympathetic:parasympathetic balance (LF/HF ratio).* Change scores RBMI and $VO_2\text{max}$ were calculated by subtracting values at six month from baseline values. Thus, a negative change in RBMI reflected weight loss and a positive change in $VO_2\text{max}$ reflected improved fitness. Changes in HRV measures were calculated by subtracting baseline values from six month values. Thus a negative change in HRV measures equated to an increase in HRV values. Spearman rho's correlation coefficients were calculated to estimate the strength and magnitude of the relationship among the change scores of the variables (RBMI).

Protection of Human Subjects

The current study and the initial study received approval from the University’s Institutional Review Board (IRB). Parents provided informed consent, and minors assented to the initial study. Risks associated with participation in the initial study included temporary muscle pain or injury or injury, and shortness of breath from exercise, pain, bruising or hematoma from blood draw, hunger due to fasting state prior to the mixed meal tolerance test, and psychological distress related to the potential identification of abnormal cardiac or metabolic abnormalities. Risks associated with the treadmill fitness testing were minimized by following the ACSM (2005) guidelines for exercise testing, having a handrail for support, and experienced investigators conducting the treadmill fitness test. When needed, arms were wrapped in a warm pad to promote vasodilation prior to venipuncture and a topical anesthetic was provided to reduce venipuncture pain. Individuals were provided with a snack following completion of the testing procedures. Interactions associated with the weight loss intervention were conducted in a respectful and supportive manner minimizing potential psychological distress to subjects. No subjects experienced a research related injury (Velasquez, personal communication). For the current study, the PI received de-identified data from the larger, initial study, thus there were no physical, social or legal risks to the subjects.
CHAPTER 4: RESULTS

The purpose of this study was to investigate the relationships among HRV, fitness, inflammation, and components of the metabolic syndrome in overweight African-American youth and examine the effect of weight loss on HRV and fitness. A secondary data analysis was conducted on 50 overweight African-American youth who participated in a supervised weight loss program. The study employed a correlational design with post-hoc analysis of pre and post-intervention data obtained from youth who participated in two arms of a weight loss, intervention program at the Youth Lifestyle Clinic at LeBonheur Medical Center. This secondary data analysis examined the prevalence of the metabolic syndrome in this group of overweight adolescents and explored relationships among HRV, fitness, inflammation, and components of the metabolic syndrome. Additionally the relationship among weight loss changes (changes in RBMI), and changes in fitness and HRV were examined. This chapter will describe the sample population using mean scores and frequency of the variables and present study results relative to each aim. All statistical analyses were performed with SAS software (version 9.1; SAS Institute, Cary, NC). \( P \) values \( \leq .05 \) were considered statistically significant.

General Sample Description

The study employed a convenience sample of 50 African-American youth from a pediatric endocrinology clinic affiliated with a large pediatric hospital in the Mid-South that were enrolled in a weight loss program. Shapedown weight loss program consisted of weekly group support and educational sessions for the subjects and their parents, in addition to routine clinic care (Mellin et al., 1987). At the beginning of the study, the subjects were between 7.2 and 18.1 years of age and all were significantly obese, with RBMI ranging from 125.6 to 337.6% RBMI, well above the 99th % percentile. Study measures were repeated after six months. A detailed description of the sample relative to each study aim is provided in the following sections that report results by study aim. The overall characteristics of the study sample are reported in Table 4.1.

Table 4.1 Characteristics of the Sample Population at Baseline

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>12.9 (2.9)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>92.2 (28.4)</td>
</tr>
<tr>
<td>RBMI (kg/m²)</td>
<td>195.5 (42.4)</td>
</tr>
<tr>
<td>Gender (%) female</td>
<td>70.0</td>
</tr>
</tbody>
</table>

SD – standard deviation,
RBMI – Relative Body Mass Index
Specific Results for Each Aim

Aim 1

Describe the prevalence of the components of the Metabolic Syndrome and the Metabolic Syndrome. To address this aim, the components of the Metabolic Syndrome were first identified, and then evaluated as to whether or not they fell within the range of their prospective normal values. The prevalence of Metabolic Syndrome components was determined by the proportion of the sample that had the risk factor divided by the total number of individuals who had data on that component. None of the participants met the criteria for type 2 diabetes mellitus. Central adiposity and insulin resistance were the most common Metabolic Syndrome components found in these subjects (Table 4.2).

Subjects were then classified as having the Metabolic Syndrome based on previously identified criteria (insulin resistance or IGT or type 2 DM plus two of the other components). The prevalence of the Metabolic Syndrome was determined by the proportion of the sample that meet the criteria for the Metabolic Syndrome divided by the total number of individuals who had data on these components. Complete data sets were not available on the entire sample, thus the prevalence of the Metabolic Syndrome was determined in a subset of 39 individuals who had complete data sets. Of these 39 youth, 46% meet the criteria for the Metabolic Syndrome. Acanthosis nigricans, a clinical sign of insulin resistance, and was found in 100% of the study sample (n = 50). If acanthosis nigricans had been used in lieu of QUICKI as an indicator of insulin resistance, 57% of the total sample would have been classified as having the Metabolic Syndrome (n = 22).

Aim 2

Describe heart rate variability, fitness levels, and levels of inflammation markers. Heart rate variability, fitness levels, and levels of inflammation markers were calculated on baseline measures. Descriptive analysis including median, ranges, mean, standard deviation, are calculated at baseline (Table 4.3). Using cut-points of 1.0 mg/L for CRP and 400 mg/dl for fibrinogen, the prevalence of elevated CRP and fibrinogen were 45% and 42%, respectively, in the total sample.

Aim 3

Explore relationships among the presence of Metabolic Syndrome components and fitness: oxygen consumption at maximal exercise (VO2max), HRV (parasympathetic function and circadian rhythmicity), and inflammation (C-reactive protein and fibrinogen) at baseline. The relationships among the presence of Metabolic Syndrome components and fitness (VO2max), heart rate variability (parasympathetic function and circadian rhythmicity), and inflammation (C-reactive protein and fibrinogen) were examined. Spearman’s rho correlation coefficients were calculated as a measure of the
Table 4.2. Presence of Metabolic Syndrome Components in Total Population

<table>
<thead>
<tr>
<th>Metabolic Syndrome Component</th>
<th>Percent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waist Circumference</td>
<td>73.33</td>
</tr>
<tr>
<td>QUICKI</td>
<td>82.05</td>
</tr>
<tr>
<td>IGT</td>
<td>17.95</td>
</tr>
<tr>
<td>HDL cholesterol &lt; 10th %tile</td>
<td>20.00</td>
</tr>
<tr>
<td>Triglyceride &gt; 90th %tile</td>
<td>40.00</td>
</tr>
<tr>
<td>Systolic Blood Pressure &gt; 90th %tile</td>
<td>44.00</td>
</tr>
</tbody>
</table>

1N = 45, 2N = 39, 3N = 50
QUICKI - quantitative insulin-sensitivity check index
IGT – impaired glucose tolerance
HDL – high density lipoprotein

Table 4.3 Baseline HRV, Fitness, and Inflammation Markers in Total Sample

<table>
<thead>
<tr>
<th>Variable</th>
<th>Median (Range)</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Rate Variability</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HF [ln(ms²)]</td>
<td>6.2 (3.2-7.3)</td>
<td>5.9 (0.9)</td>
</tr>
<tr>
<td>SDNN (ms)</td>
<td>124.0 (57.0-234.0)</td>
<td>128.1 (38.2)</td>
</tr>
<tr>
<td>LF/HF ratio</td>
<td>1.1 (1.0-1.6)</td>
<td>1.1 (0.1)</td>
</tr>
<tr>
<td>Fitness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VO₂ max (mg/kg/min)</td>
<td>18.3 (13.5-31.9)</td>
<td>18.8 (4.5)</td>
</tr>
<tr>
<td>Inflammation Markers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-reactive protein (mg/L)</td>
<td>0.41 (0.03-8.80)</td>
<td>0.75 (1.34)</td>
</tr>
<tr>
<td>Fibrinogen (mg/dl)</td>
<td>365.0 (205.0-560.0)</td>
<td>372.64 (71.12)</td>
</tr>
</tbody>
</table>

SD – standard deviation
HF – high frequency
SDNN – standard deviation of R-R intervals of QRS complexes of normal beats
LF/HF – low frequency/high frequency
VO₂ max – oxygen consumption at maximal exercise
strength and magnitude of the relationship among HRV, fitness, inflammation markers and severity of obesity.

Higher fitness (VO2max) was significantly associated with higher HRV measures of parasympathetic function (HF) and circadian rhythmicity (SDNN), and lower levels of fibrinogen (Table 4.4). Severity of obesity (RBMI) was not associated with HRV measures, while higher RBMI was associated with poorer fitness (VO2max), and higher levels of inflammation (CRP and fibrinogen). Higher CRP was associated with higher fibrinogen levels (Table 4.4).

Because cut-points for Metabolic Syndrome components vary by age, correlations among raw values of Metabolic Syndrome components and other measures may be less meaningful. Thus, subjects were classified into two groups based on the presence of specific Metabolic Syndrome components and nonparametric t-tests (Mann-Whitney U) were used to evaluate potential differences in HRV, fitness, and inflammation markers between Metabolic Syndrome component groups. The level of significance was set at 0.05.

Individuals with impaired glucose tolerance did not differ in HRV measures, fitness, or level of inflammation markers (Table 4.5). The presence of insulin resistance was associated with higher parasympathetic function and higher levels of inflammation (Table 4.6). Central adiposity was associated with a lower sympathetic: parasympathetic balance (LF/HF ratio) (Table 4.7). Lower HDL-cholesterol levels were associated with higher levels of fibrinogen (Table 4.8). Neither the presence of hypertension nor elevated triglycerides was associated with decreased HRV measures, lower fitness, or higher levels of inflammation markers (Tables 4.9 and 4.10).

HRV, fitness and inflammation markers were compared in subjects with the Metabolic Syndrome and without the Metabolic Syndrome. Regardless of whether QUICKI or acanthosis nigricans were used as a measure of insulin resistance, there were no significant differences in HRV, fitness, or inflammation markers between those with or without the Metabolic Syndrome (Tables 4.11 and 4.12).

Aim 4

*Explore the effect of age, gender, and baseline fitness on weight loss (change in Relative Body Mass Index (RBMI)).* Six-month post-data were available on 39 individuals in the weight loss study. Characteristics of these individuals are summarized in Table 4.13.

In the subset of these obese 39 African-American youth who completed the weight loss intervention, the effect of age, gender, and baseline fitness on weight loss (change in RBMI and percentage of baseline RBMI lost) was examined. Multiple linear regression analysis was used to determine if demographic variables of age, gender, baseline fitness (VO2max), or an interaction among those variables could explain a
Table 4.4. Correlation Coefficients among HRV Measures, Fitness, Inflammation Markers, and Severity of Obesity in the Total Sample

<table>
<thead>
<tr>
<th>Measures</th>
<th>Fitness</th>
<th>Inflammation Markers</th>
<th>Obesity Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>VO$_{2\text{max}}$</td>
<td>CRP</td>
<td>Fibrinogen</td>
</tr>
<tr>
<td>Heart Rate Variability</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HF</td>
<td>r = 0.41</td>
<td>-0.27</td>
<td>-0.17</td>
</tr>
<tr>
<td></td>
<td>p = 0.004</td>
<td>0.08</td>
<td>0.30</td>
</tr>
<tr>
<td>SDNN</td>
<td>r = 0.39</td>
<td>-0.21</td>
<td>-0.18</td>
</tr>
<tr>
<td></td>
<td>p = 0.007</td>
<td>0.17</td>
<td>0.24</td>
</tr>
<tr>
<td>LF/HF ratio</td>
<td>r = -0.06</td>
<td>0.19</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>p = 0.71</td>
<td>0.21</td>
<td>0.83</td>
</tr>
<tr>
<td>Fitness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VO$_{2\text{max}}$</td>
<td>r = -----</td>
<td>-0.16</td>
<td>-0.53</td>
</tr>
<tr>
<td></td>
<td>p = 0.30</td>
<td>0.0002</td>
<td>0.0007</td>
</tr>
<tr>
<td>Inflammation Markers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP</td>
<td>r = -----</td>
<td>0.30</td>
<td>0.38</td>
</tr>
<tr>
<td></td>
<td>p = 0.04</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>r = ----</td>
<td>0.51</td>
<td></td>
</tr>
<tr>
<td></td>
<td>p = 0.003</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HF – high frequency
SDNN – standard deviation of R-R intervals of QRS complexes of normal beats
LF/HF – low frequency/high frequency
VO$_{2\text{max}}$ – oxygen consumption at maximal exercise
CRP – C-reactive protein
r – relationship
p – probability
RBMI – relative body mass index
Table 4.5. Differences in HRV, Fitness, and Inflammation Markers Based on Presence of Impaired Glucose Tolerance (IGT)

<table>
<thead>
<tr>
<th>Groups Based on IGT</th>
<th>HRV Measures</th>
<th>Fitness</th>
<th>Inflammation Markers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HF Median (range)</td>
<td>SDNN Median (range)</td>
<td>LF/HF Ratio Median (range)</td>
</tr>
<tr>
<td>Yes (n = 7)</td>
<td>6.14 (3.97, 6.85)</td>
<td>128 (86, 155)</td>
<td>1.08 (1.00, 1.24)</td>
</tr>
<tr>
<td>Normal (n = 31)</td>
<td>6.18 (4.47, 7.75)</td>
<td>119 (77, 234)</td>
<td>1.05 (0.96, 1.22)</td>
</tr>
</tbody>
</table>

P-value 0.23 0.59 0.21 0.35 0.11 0.36

IGT – impaired glucose tolerance
HF – high frequency
HRV – heart rate variability
SDNN - standard deviation of R-R intervals of QRS complexes of normal beats
LF/HF – low frequency/high frequency
VO_{2max} – oxygen consumption at maximal exercise
CRP – C-reactive protein
Table 4.6. Differences in HRV, Fitness, and Inflammation Based on Insulin Resistance

<table>
<thead>
<tr>
<th>Insulin Resistance (QUICKI)</th>
<th>HRV Measures</th>
<th>Fitness</th>
<th>Inflammation Markers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HF Median</td>
<td>SDNN Median</td>
<td>LF/HF Ratio Median</td>
</tr>
<tr>
<td>Yes (n = 31)</td>
<td>6.22 (3.97, 7.75)</td>
<td>124 (77, 234)</td>
<td>1.06 (0.96, 1.24)</td>
</tr>
<tr>
<td>Normal (n = 7)</td>
<td>5.96 (4.73, 6.55)</td>
<td>115 (88, 131)</td>
<td>1.09 (0.98, 1.18)</td>
</tr>
<tr>
<td>P-value</td>
<td>0.004</td>
<td>0.21</td>
<td>0.20</td>
</tr>
</tbody>
</table>

QUICKI – quantitative insulin-sensitivity check index
HF – high frequency
HRV – heart rate variability
SDNN - standard deviation of R-R intervals of QRS complexes of normal beats
LF/HF – low frequency/high frequency
VO\textsubscript{2max} – oxygen consumption at maximal exercise
CRP – C-reactive protein
Table 4.7. Differences in HRV, Fitness, and Inflammation Based on Metabolic Syndrome Component of Central Adiposity

<table>
<thead>
<tr>
<th>Groups Based on Central Adiposity</th>
<th>HRV Measures</th>
<th>Fitness</th>
<th>Inflammation Markers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HF Median (range)</td>
<td>SDNN Median (range)</td>
<td>LF/HF Ratio Median (range)</td>
</tr>
<tr>
<td>Yes (n = 32)</td>
<td>6.20 (3.97, 7.75)</td>
<td>124 (77, 134)</td>
<td>1.05 (0.96, 1.24)</td>
</tr>
<tr>
<td>No (n = 12)</td>
<td>5.98 (3.20, 6.69)</td>
<td>123.5 (57, 159)</td>
<td>1.10 (0.98, 1.57)</td>
</tr>
<tr>
<td>P-value</td>
<td>0.13</td>
<td>0.74</td>
<td>0.02</td>
</tr>
</tbody>
</table>

HF – high frequency
HRV – heart rate variability
SDNN - standard deviation of R-R intervals of QRS complexes of normal beats
LF/HF – low frequency/high frequency
VO<sub>2max</sub> – oxygen consumption at maximal exercise
CRP – C-reactive protein
Table 4.8. Differences in HRV, Fitness, and Inflammation Based on Metabolic Syndrome Component of HDL-cholesterol

<table>
<thead>
<tr>
<th>Groups Based on HDL</th>
<th>HRV Measures</th>
<th>Fitness</th>
<th>Inflammation Markers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HF Median (range)</td>
<td>SDNN Median (range)</td>
<td>LF/HF Ratio Median (range)</td>
</tr>
<tr>
<td>Abnormal (n = 9)</td>
<td>6.18 (4.73, 6.58)</td>
<td>115 (85, 234)</td>
<td>1.09 (0.98, 1.22)</td>
</tr>
<tr>
<td>Normal (n = 36)</td>
<td>6.20 (3.97, 7.75)</td>
<td>128 (77, 192)</td>
<td>1.06 (0.96, 1.24)</td>
</tr>
<tr>
<td>P-value</td>
<td>0.65</td>
<td>0.22</td>
<td>0.23</td>
</tr>
</tbody>
</table>

HDL – high density lipoprotein
HF – high frequency
HRV – heart rate variability
SDNN - standard deviation of R-R intervals of QRS complexes of normal beats
LF/HF - low frequency/high frequency
VO$_{2\text{max}}$ – oxygen consumption at maximal exercise
CRP – C-reactive protein
Table 4.9. Differences in HRV, Fitness, and Inflammation Based on Metabolic Syndrome Component of Elevated Systolic Blood Pressure

<table>
<thead>
<tr>
<th>Groups Based on Systolic Blood Pressure</th>
<th>HRV Measures</th>
<th>Fitness</th>
<th>Inflammation Markers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HF Median (range)</td>
<td>SDNN Median (range)</td>
<td>LF/HF Ratio Median (range)</td>
</tr>
<tr>
<td>High (n = 22)</td>
<td>6.20 (3.2, 7.30)</td>
<td>128 (57, 192)</td>
<td>1.10 (1.00, 1.60)</td>
</tr>
<tr>
<td>Normal (n = 27)</td>
<td>6.20 (4.00, 7.8)</td>
<td>124.5 (85, 234)</td>
<td>1.0 (1.0, 1.2)</td>
</tr>
<tr>
<td>P-value</td>
<td>0.52</td>
<td>0.78</td>
<td>0.26</td>
</tr>
</tbody>
</table>

HF – high frequency  
HRV – heart rate variability  
SDNN - standard deviation of R-R intervals of QRS complexes of normal beats  
LF/HF – low frequency/high frequency  
VO\(_{2\text{max}}\) – oxygen consumption at maximal exercise  
CRP – C-reactive protein
Table 4.10. Differences in HRV, Fitness and Inflammation Based on Metabolic Syndrome Component of Triglycerides

<table>
<thead>
<tr>
<th>Groups Based on Triglycerides</th>
<th>HRV Measures</th>
<th>Fitness</th>
<th>Inflammation Markers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HF Median (range)</td>
<td>SDNN Median (range)</td>
<td>LF/HF Ratio Median (range)</td>
</tr>
<tr>
<td>Abnormal (n = 18)</td>
<td>6.30 (3.97, 7.75)</td>
<td>120 (85, 192)</td>
<td>1.06 (1.00, 1.24)</td>
</tr>
<tr>
<td>Normal (n = 27)</td>
<td>6.18 (4.73, 7.20)</td>
<td>129.5 (85, 234)</td>
<td>1.08 (0.96, 1.21)</td>
</tr>
<tr>
<td>P-value</td>
<td>0.65</td>
<td>0.69</td>
<td>0.90</td>
</tr>
</tbody>
</table>

HF – high frequency
HRV – heart rate variability
SDNN - standard deviation of R-R intervals of QRS complexes of normal beats
LF/HF – low frequency/high frequency
VO$_{2\text{max}}$ – oxygen consumption at maximal exercise
CRP – C-reactive protein
Table 4.11. Differences in HRV, Fitness and Inflammation Based on the Presence of the Metabolic Syndrome Using QUICKI as the Measure of Insulin Resistance

<table>
<thead>
<tr>
<th>Metabolic Syndrome</th>
<th>HF Median (range)</th>
<th>SDNN Median (range)</th>
<th>LF/HF Ratio Median (range)</th>
<th>VO₂max Median (range)</th>
<th>CRP Median (range)</th>
<th>Fibrinogen Median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes (n = 18)</td>
<td>6.17 (3.20, 7.75)</td>
<td>124 (57, 234)</td>
<td>1.06 (1.00, 1.29)</td>
<td>18.2 (12.1, 31.9)</td>
<td>0.30 (0.03, 8.80)</td>
<td>369 (205, 560)</td>
</tr>
<tr>
<td>No (n = 21)</td>
<td>7.63 (4.02, 7.20)</td>
<td>129.0 (68, 191)</td>
<td>1.08 (0.99, 1.15)</td>
<td>20.8 (14.7, 27.7)</td>
<td>0.11 (0.05, 0.20)</td>
<td>322 (234, 400)</td>
</tr>
<tr>
<td>P-value</td>
<td>0.64</td>
<td>0.85</td>
<td>0.94</td>
<td>0.54</td>
<td>0.93</td>
<td>0.25</td>
</tr>
</tbody>
</table>

HF – high frequency
HRV – heart rate variability
SDNN - standard deviation of R-R intervals of QRS complexes of normal beats
LF/HF – low frequency/high frequency
VO₂max – oxygen consumption at maximal exercise
CRP – C-reactive protein
Table 4.12. Differences in HRV, Fitness and Inflammation Based on the Presence of the Metabolic Syndrome Using Acanthosis Nigricans as the Measure of Insulin Resistance

<table>
<thead>
<tr>
<th>Metabolic Syndrome</th>
<th>HRV Measures</th>
<th>Fitness</th>
<th>Inflammation Markers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HF Median (range)</td>
<td>SDNN Median (range)</td>
<td>LF/HF Ratio Median (range)</td>
</tr>
<tr>
<td>Yes (n = 24)</td>
<td>6.31 (3.97, 7.75)</td>
<td>125 (65, 234)</td>
<td>1.05 (0.96, 1.27)</td>
</tr>
<tr>
<td>No (n = 19)</td>
<td>5.87 (3.20, 7.06)</td>
<td>128.1 (57, 191)</td>
<td>1.09 (0.98, 1.57)</td>
</tr>
<tr>
<td>P-value</td>
<td>0.92</td>
<td>0.89</td>
<td>0.45</td>
</tr>
</tbody>
</table>

HF – high frequency
HRV – heart rate variability
SDNN - standard deviation of R-R intervals of QRS complexes of normal beats
LF/HF – low frequency/high frequency
VO2max – oxygen consumption at maximal exercise
CRP – C-reactive protein
Table 4.13. Characteristics of the Sub-sample at the 6 Month Time Point

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>13.6 (2.8)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>94.3 (25.8)</td>
</tr>
<tr>
<td>RBMI</td>
<td>195.0 (38.9)</td>
</tr>
<tr>
<td>Gender (%) female</td>
<td>74.36</td>
</tr>
</tbody>
</table>

SD – standard deviation
RBMI – relative body mass index
significant proportion of the weight loss variance. Variables were removed from the model in a backwards fashion, with those retained in the model having a p value of 0.05 or less. Change in RBMI was used as the weight loss measure and calculated by subtracting the 6-month RBMI value from the baseline value. Male gender and higher baseline fitness predicted weight loss, accounting for 28% of the variance in RBMI change ($R^2 = 0.28$, model $p = 0.0028$).

**Aim 5**

*Correlations among changes scores.* Change scores RBMI and $VO_{2\text{max}}$ were calculated by subtracting values at six month from baseline values. Thus, a negative change in RBMI reflected weight loss and a positive change in $VO_{2\text{max}}$ reflected improved fitness. Changes in HRV measures were calculated by subtracting baseline values from 6-month values. Thus a negative change in HRV measures equated to an increase in HRV values. Spearman rho's correlation coefficients were used to estimate the strength and magnitude of the relationship among the weight loss, fitness and HRV change scores (Table 4.14).

Weight loss, defined as change in RBMI, was significantly associated with increased circadian rhythmicity (SDNN) ($p = 0.04$), and there was trend for weight loss to be associated with improvements in $VO_{2\text{max}}$ ($p = 0.07$) and improved parasympathetic function ($p = 0.07$). Change in fitness was not significantly associated with changes in HRV measures.

<table>
<thead>
<tr>
<th>Measure</th>
<th>$\Delta VO_{2\text{max}}$</th>
<th>$\Delta HF$</th>
<th>$\Delta LF/HF \text{ ratio}$</th>
<th>$\Delta SDNN$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\Delta RBMI$</td>
<td>$r = -0.30$</td>
<td>$0.33$</td>
<td>$-0.21$</td>
<td>$0.36$</td>
</tr>
<tr>
<td></td>
<td>$p = 0.07$</td>
<td>$0.07$</td>
<td>$0.23$</td>
<td>$0.04$</td>
</tr>
<tr>
<td>$\Delta VO_{2\text{max}}$</td>
<td>$r = -0.13$</td>
<td>$-0.05$</td>
<td>$-0.22$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$p = 0.48$</td>
<td>$0.79$</td>
<td>$0.21$</td>
<td></td>
</tr>
</tbody>
</table>

$VO_{2\text{ max}}$ – oxygen consumption at maximal exercise
HF – high frequency
LF/HF – low frequency/high frequency
SDNN – standard deviation of R-R intervals of QRS complexes of normal beats
RBMI – relative body mass index
CHAPTER 5: DISCUSSION, RECOMMENDATIONS, AND CONCLUSIONS

Childhood obesity has been linked to the Metabolic Syndrome. The Metabolic Syndrome is characterized by a clustering of risk factors, including obesity, hypertension, dyslipidemia, glucose intolerance and insulin resistance, and has been identified as a precursor to both CVD and T2DM (Lorenzo, Williams, et al., 2007; Morrison, et al., 2008). The relationships among the Metabolic Syndrome to inflammation, HRV, and fitness in obese youth are understudied. Therefore, the purpose of this study was to explore the relationships among HRV, inflammation, fitness, and components of the Metabolic Syndrome in obese African-American youth participating in a supervised weight management program and examine the effect of weight loss on HRV and fitness. Additionally, age, gender, and baseline fitness levels as predictors of weight loss were explored. Chapter five provides a discussion of the study findings relevant to each research aim and provides implications for theory, practice, policy and research.

Discussion of Specific Aims

Aim 1

The first specific aim was to describe the prevalence of the Metabolic Syndrome and Metabolic Syndrome components in a cohort of obese African-American youth. Although the Metabolic Syndrome is a well-recognized clinical phenomenon, there is no internationally accepted definition. Metabolic Syndrome is also known as dysmetabolic syndrome, syndrome X, insulin resistance syndrome, obesity syndrome, Reaven’s syndrome (Moller et al., 1991) and most recently cardiometabolic syndrome. Described in 1988 as a cluster of symptoms, Metabolic Syndrome is a set of risk factors that includes: abdominal obesity, a decreased ability to process glucose, dyslipidemia, and hypertension (Reavens, 1988), and more recently, cardiovascular inflammatory and prothrombotic markers (Sutherland, McKinley, & Eckel, 2004) have been suggested. These are risk factors for atherosclerotic cardiovascular disease (CVD) and type 2 diabetes (Steinberger, 2003).

Among adolescents with high intra-abdominal fat, the Metabolic Syndrome (based on NCEP) was found in 13.8% of the boys and 8.3% of the girls (Syme et al., 2008), and in severely obese adolescents, the prevalence of the Metabolic Syndrome is nearly 50% (Spiotta & Luma, 2008; Weiss et al., 2004). In the present study of obese African-American youth, which included children ages 7-18, 46.15% meet criteria for the Metabolic Syndrome which is consistent with results reported by both Spiotta and Luma and also Weiss et al. (2004) in severely obese adolescents. However, only 78% of the total sample had data sets that included QUICKI and glucose values which were necessary for determining Metabolic Syndrome status. Using acanthosis nigricans in lieu of QUICKI as an indicator of insulin resistance, an alarming 57% of the total sample was classified as having the Metabolic Syndrome. Interestingly, the younger age of participants included in this study did not result in a lower prevalence of Metabolic Syndrome.
compared to other studies which excluded younger children. Velasquez-Mieyer and colleagues (2008) reported that a QUICKI value > 0.3 correlated with glucose intolerance in obese youth. Whether that cut-point is appropriate for determination of insulin resistance requires further investigation.

The prevalence of Metabolic Syndrome components of insulin resistance, glucose intolerance, T2DM, central adiposity, low HDL-cholesterol, high triglycerides, and systolic hypertension were examined in study participants. Insulin resistance (82.05%) and central adiposity (73.33%) were the most common Metabolic Syndrome components identified. Impaired glucose tolerance and T2DM were the least prevalent components (17.95% and 0%, respectively). These results are in agreement with others (Shalitin, Abrahami, Lilos, & Phillip, 2005) who found insulin resistance in 81.2% of their obese patients and impaired glucose tolerance in only 13.5%.

Central adiposity was determined by waist circumference. The average waist circumference was 95.9 cm, with males having a slightly larger mean waist circumference than females (96.88 cm vs. 96.33 cm). Subjects were classified as having an elevated waist circumference if values exceeded the 90th percentile for age and race based on reference values developed by Fernandez et al. (2004). In their reference guide, the average waist circumference in the 90th percentile for African-American males between the ages of 7 and 18 years was 83.75 cm and for females 88.7 cm. The high prevalence of central adiposity in the current study may be a reflection of the severity of obesity in the subject population. The mean RBMI, a measure of overweight severity in children (Velasquez-Mieyer, Perez-Faustinelli, & Cowan, 2005), for the subjects in this study was 195.5% with a range of 125.6-337.6%, suggesting that the majority of subjects in this study were severely obese.

Lipid abnormalities were less prevalent than expected; elevated triglycerides occurred in 40%, and decreased HDL cholesterol was present in 20% of the subjects. However lipid abnormalities were more common than reported in other studies. Jago and colleagues (2006) found lipid abnormalities in only 12–17% of overweight and obese 8th graders. The prevalence of risk factors in their study differed by age and gender (Jago et al.), however, subgroup analysis by age and gender was not undertaken in the current study due to the wide-range of age and small numbers in each age category. It would seem plausible that the inclusion of older and more obese youth in the present study, and therefore the longer exposure to excess body fat, would affect the accumulation of lipids in the blood stream. In the present study, the determination of abnormal triglyceride and HDL cholesterol levels were based upon age and gender specific normative values developed from data collected during the Third National Health and Nutrition Examination Survey (Hickman, et al., 1998). In contrast, Jago and colleagues used a lower cut-point for abnormal HDL cholesterol developed by the National Cholesterol Education Program in 1992, resulting in fewer youth being classified as having abnormal HDL cholesterol. Additionally, subjects in the present study were in the lower fitness strata (VO2max X = 18.8), which may have attributed to the higher prevalence of abnormal HDL cholesterol found in this study compared to previous studies (Jago et al.). Higher levels of fitness and physical activity are associated with higher HDL cholesterol levels.
(Eisenmann, 2004; Manios et al., 2005). The use of different cut-points for determining elevated triglycerides may have contributed to the difference in prevalence of triglycerides reported by Jago and colleagues (2006) and in the current study. Based on the criteria of Cook and associates (2003), Jago et al. defined abnormal triglycerides as a value >110 mg/dL. In the current study, a triglyceride level of above the 90th percentile (101 mg/dl) for African-American adolescents was used (Hickman, et al, 1998), which may be one factor contributing to the higher percentage of elevated triglyceride levels found in this population. Additionally elevated triglycerides levels are associated with diabetes and IGT (Newfield, Dewan, & Jain, 2008). While none of the subjects in the current study had diabetes, 17.95% had IGT which may influence triglyceride levels.

Childhood obesity is linked to hypertension. Sorof and associates (2004) reported that obese children had a 3.26 higher relative risk for hypertension, with other researchers found that 41.5% (Bueno et al., 2007) to 61% (Velasquez-Mieyer, Neira, et al., 2007) of obese youth exhibited hypertension. Given the young age of participants in the current study a prevalence rate of 44% in obese youth is a cause for concern. Hypertension is the leading cause of renal failure in African Americans and weight loss is the only recommended treatment for obesity-induced hypertension (Ferdinand, 2006).

In summary the Metabolic Syndrome was defined using WHO criteria as its foundation and the values of the components were based on the latest normative values. The lack of common criteria and cut-points among studies makes comparisons difficult and sometimes ambiguous. Generally the findings in the present study are consistent with previous studies regarding the prevalence of Metabolic Syndrome and its components in obese youth.

Aim 2

Specific aim 2 was to describe heart rate variability, fitness levels, and levels of inflammation in this cohort of obese African-American youth. HRV measures are increasingly used in research to assess the cardiovascular system in youth with obesity (Chen, Lee, Chiu, & Jeng, 2007; Kaufman, Kaiser, Steinberger, Kelly, & Dengel, 2007), diabetes (Faulkner et al., 2001), and cardiac anomalies (Massin & von Bernuth, 1998). The average parasympathetic tone (HF) and measures of circadian fluctuation (SDNN) at baseline were lower than values previously reported in normal controls (Goto et al., 1997), obese youth (Gutin, Yin et al., 2005), and adolescents with diabetes (Faulkner et al., 2001) suggesting greater impairment of autonomic function in this sample. The current study included subjects of varying ages and gender, as well as low fitness level, which may have contributed to the poorer values seen in this study.

Sympathetic:parasympathetic balance (LF/HF) was higher than reported by Gutin, Howe et al. (2005) in obese adolescents, indicating sympathetic predominance in youth participating in the current study. Kaufman and associates (2007) reported that obese 10 to 13 year olds exhibited significantly higher LF/HF ratio indicating sympathetic predominance and lower parasympathetic measures (HF) compared to normal weight.
children, with a trend \( (p < 0.07) \) toward lower measures of circadian fluctuation (SDNN). However, the obese children were also more insulin resistant and had higher systolic blood pressures (Kaufman et al., 2007). While none of the subjects had diabetes, a study of diabetic youth, females and those with higher BMI, poorer glucose control, and lower amounts of physical activity tended to have poorer HRV values (Faulkner et al., 2005). In the current study, subjects were more severely obese, less fit, and had a high prevalence of insulin resistance than reported in previous studies which may have contributed to the low HRV values found in this study sample.

Adult studies suggest that African Americans have lower HF and LF/HF ratio than Caucasians (Choi et al., 2006). However, African-American subjects in Choi’s study had a higher average BMI than the Caucasian subjects which may have contributed to these racial differences. The lower HRV values found in the African-American youth participating in the current study may have resulted from a gender effect (Brunetto, Roseguini, Silva, Hirai, & Guedes, 2005; Silvetti, Drago, & Ragonese, 2001), differences in physical activity, race (Choi et al., 2006; Kim et al., 2006), age (Silvetti et al.), or body mass index (Faulkner, et al., 2003). Future examination of the relationship between age, gender, race, obesity severity, and physical activity on HRV measures in youths is needed.

As expected, overall fitness was poor. Normative values for VO\(_{2}\)max (fitness) based on age and gender have been reported (Boardley, Sargent, Coker, Hussey, & Sharpe, 1995; Eiberg et al., 2005; Heyward, 1998; Hussey, Bell, Bennett, O'Dwyer, & Gormley, 2007). In the current sample of obese youth, VO\(_{2}\)max ranged from 13.5-31.9 mg/kg/min with a mean value of 18.8 mg/kg/min (SD = 4.5), which was far lower than those values reported in a sample of normal weight, overweight and obese youth by Gutin and associates (2005). Calculation of VO\(_{2}\)max (ml/kg/min) involves dividing oxygen consumption by weight, thus it is not surprising that fitness values were low given the severity of obesity found in the sample. However, obesity does not preclude fitness, and large cohort studies support the benefit of physical activity and fitness in attenuating the risk of cardiovascular and all-cause mortality in overweight and obese adults.(Blair & Brodney, 1999; Farrell et al., 1999; Wei et al., 1999a).

Inflammation, CRP and fibrinogen levels, was measured in the present cohort. Using cut-points of 1.0 mg/L for CRP and 400 mg/dl for fibrinogen, the prevalence of elevated CRP and fibrinogen were 45% and 42% respectively in the total sample. In contrast, a recent study, examining NHANES 1999-2004 data obtained from children and adolescents, found less than 10% of youth had high-sensitivity CRP levels > 3mg/L with higher CRP values (> 3 mg/L) associated with higher BMI values, higher SBP values, and lower HDL cholesterol levels, increasing age, and minority race/ethnicity (Lande, Pearson, Vermilion, Auinger, & Fernandez, 2008). Using data from 1,366 adolescents who participated in the NHANES 1999-2000, Ford and colleagues (2005) reported that 38.4% of those with the Metabolic Syndrome had a CRP > 3.0 mg/L compared to 10.3% of those without the syndrome (Ford, Ajani, & Mokdad, 2005). In contrast, the prevalence of an elevated CRP value (not high sensitivity CRP) in obese youth participating in this study was 45% regardless of whether the Metabolic Syndrome was
present. Since this study was conducted, there has been a move toward assessing high-sensitivity CRP, also called CPR cardiac, as a measure of cardiovascular risk. However, the CRP used in this study is a marker of general inflammation which may be important for determining risk for diabetes. Whether the cut-points used in the current study predict future risk of obese youth to develop cardiovascular disease or T2DM is unknown.

Greater impairment of autonomic function found in this sample compared to previous studies (Faulkner et al., 2001; Goto et al., 1997; Gutin, Yin et al., 2005) may be contributed to the wide variance of ages, overall low fitness level and the greater percent of females in the sample. Prospective studies are needed to clarify the influence the effect of weight, age, gender, and race on heart rate variability measures in youth.

Aim 3

**Relationships among heart rate variability, fitness and inflammation.** The first objective of specific aim 3 was to explore relationship among heart rate variability measures of parasympathetic function (HF), circadian rhythmicity (SDNN), sympathetic:parasympathetic balance (LF/HF ratio), fitness (VO\textsubscript{2max}) and inflammation (CRP and fibrinogen) at baseline. Data from the current study indicate higher fitness (VO\textsubscript{2max}) was significantly associated with higher HRV measures of parasympathetic function (HF) and circadian rhythmicity (SDNN), and lower levels of fibrinogen. Severity of obesity (RBMI) was not associated with HRV measures, while higher RBMI was associated with poorer fitness (VO\textsubscript{2max}), and higher levels of inflammation (CRP and fibrinogen). Higher CRP was associated with higher fibrinogen levels.

It was postulated that higher fitness is associated with better HRV measures and less inflammation. Regular physical activity and higher fitness levels have been linked to higher heart rate variability, particularly measures of parasympathetic function, in adults and youth, with and without obesity (Buchheit, 2007; Davy et al., 1998; De Meersman, 1993; Gutin et al., 1997; Levy et al., 1998; Muller et al., 2008; Notarius, Levy, Tully, Fitchett, & Magder, 1998). In contrast, Brunetto and associates (2005) did not find any significant relationship between HRV measures and fitness in their adolescent subjects. In this study, of low-fit obese youth, higher fitness (VO\textsubscript{2max}) was significantly associated with higher HRV measures of parasympathetic function (HF) and circadian rhythmicity (SDNN), but not sympathetic-parasympathetic balance (LF/HF ratio). Sympathetic-parasympathetic balance may be more strongly influenced by adiposity as adipocytes release vasoactive substances which elicit sympathetic activity. However, in this sample of obese youth, severity of obesity was not significantly associated with the LF/HF ratio, which may be a reflection of low fitness.

Previous research suggests that higher fitness levels are associated with lower levels of inflammation (Kuo et al., 2007) and exercise training reduces inflammatory markers independent of adiposity in adults (Thomas, Baker, Graham, Cooper, & Davies, 2008). In contrast, studies in youth suggest that adiposity is the major determinant of inflammatory levels in children although physical fitness has a smaller independent effect.
(Cook et al., 2000; Ruiz et al., 2007). In the present study, higher fitness (VO$_{2\text{max}}$) was significantly correlated with lower fibrinogen ($p = 0.007$) but not CRP levels ($p = 0.30$). These results are in agreement with findings by Cook and colleagues, (2000) who found that fibrinogen was negatively correlated with fitness. In the current study, higher severity of obesity was associated with higher CRP and fibrinogen values. Studies in youth have found that obese children exhibit significantly higher concentrations of fibrinogen and other inflammatory cytokines (ferritin, IL-6, and TNF) (Halle et al., 2004) than non-obese children, with adiposity being significantly associated with CRP levels in young adolescents (Thomas et al., 2008). These results suggest that severity of obesity already effects inflammation which is a component of adult heart disease and possible early death. This is note-worthy because increased fitness, even in the presence of obesity, may be a protector from cardiovascular disease, injury and death (Farrell et al., 2002; Farrell, Cortese, LaMonte, & Blair, 2007; Lee et al., 1999; Wei, Gibbons, Kampert, Nichaman, & Blair, 2000; Wei et al., 1999).

**Relationships among Metabolic Syndrome, HRV, fitness, and inflammation.**
The second purpose of aim 3 was to explore the relationship of HRV, fitness, and inflammation with the presence or absence of the Metabolic Syndrome and its markers: IGT, IR, central obesity, HTN, HDL, TG, at baseline. It was hypothesized that the presence of the Metabolic Syndrome or components of the Metabolic Syndrome (impaired glucose tolerance, insulin resistance, central adiposity, elevated blood pressure, elevated triglycerides and low HDL-cholesterol) would be associated with lower measures of parasympathetic function, fitness and higher levels of inflammation.

**Metabolic Syndrome and HRV.** HRV measures, fitness and inflammatory markers were not associated with the Metabolic Syndrome regardless of whether QUICKI or acanthosis nigrican were used as the measure of insulin resistance. Studies comparing HRV in youth with and without the Metabolic Syndrome were not found in the literature. One study examining HRV and Metabolic Syndrome in Japanese adults found that HRV indices in the group with Metabolic Syndrome were significantly lower than those in the group without Metabolic Syndrome (Min, Min, Paek, & Cho, 2008) with HRV gradually decreasing as the number of the number of Metabolic Syndrome components increased.

The association of HRV measures to Metabolic Syndrome criteria of IGT, insulin resistance, central adiposity, elevated blood pressure, elevated triglycerides and low HDL-cholesterol were examined in the current study. There were no differences in HRV measures in those with IGT. These findings differ from those reported in adult studies. Research in adults suggests a weak relationship between pre-diabetes (fasting glucose) and heart rate variability measures (Schroeder et al., 2005). Work by (Singh et al., 2000) revealed that fasting blood glucose levels were inversely correlated with HRV measures of SDNN, HF, and LF ($r = -0.21$ to $-0.26$). After adjusting for the clinical covariates, statistically significant differences in only LF/HF ratio (measures of sympathetic: parasympathetic balance) remained between the normal glucose tolerance groups and those with diabetes. While the impaired glucose tolerance group continued to have poorer HRV measures compared to the normal glucose group, these differences were not
statistically significant (Singh et al., 2000). Stein and colleagues (2007) found no significant differences in HRV measures between adults with normal fasting glucose levels and those with impaired fasting glucose (fasting blood glucose ranging from 5.6–6.0 mmol/L). In contrast, they reported that individuals with higher fasting glucose levels (6.1–6.9 mmol/L) had HRV values similar to adults with diabetes, which were lower than those found in the normal glucose group. In the current study, the lack of differences in HRV values found between obese youth with IGT and those with normal glucose tolerance may be partially attributed to the modest elevations in fasting glucose found within the IGT group.

Postprandial insulin hypersecretion is postulated to be driven by parasympathetic activation of the pancreatic beta cells through the pancreatic branch of the vagus nerve (Lustig et al., 2003). Obesity is usually associated with increased sympathetic nervous system activity. Chronic sympathetic stimulation may inhibit insulin secretion from the beta cells (Carnethon et al., 2006), further contributing to insulin resistance and impaired glucose tolerance. Unexpectedly, HRV measures of parasympathetic function (HF) were lower in obese African-American youth without insulin resistance. Potential differences in age, gender and fitness status may have contributed to the unexpected findings. Perciaccante and colleagues (2006) reported that insulin resistance was linked to lower SDNN values. However, the current study did not find differences in SDNN between groups. The cut-point for insulin resistance in the current study was based upon previous work by Velasquez-Meyer and colleagues (2007) in which a QUICKI value < 0.3 was associated with impaired glucose tolerance. Further work is needed to determine if this cut-point is relevant as a normative value for insulin resistance.

Interestingly, individuals without central adiposity exhibited higher LF:HF ratios, reflecting sympathetic predominance. The pattern of sympathetic and parasympathetic dysfunction may be affected by the duration of obesity. Obese adolescents (n = 50) were stratified based on duration of obesity and compared to 12 lean peers (Rabbia et al., 2003). Compared to the normal weight group, only the recently obese group exhibited a significantly higher LF:HF ratio reflecting sympathetic predominance, while those with greater duration of obesity exhibited similar LF:HF ratio to the normal weight group (Rabbia et al., 2003). In the present study, the duration of obesity was unknown and those with central adiposity were significantly younger (p < 0.01) than those without central adiposity which may contribute to differences in LF:HF between groups.

Neither high SBP nor lipid abnormalities (low HDL-cholesterol and elevated triglycerides) were associated with HRV measures. Others have reported that increased sympathetic tone (Sorof & Daniels, 2002) and reduced parasympathetic tone (Gutin et al., 2000) were linked to hypertension in obese youth. Our findings are contrary to what was expected as hypertension is suspected to be an outcome of the regulation of the autonomic nervous system. However in adults, there was no measurable difference in the rate of change in heart rate variability among those with and without hypertension (Schroeder et al., 2003) in a 9 year follow-up study. Heart rate variability measures of SDNN are decreased in adult subjects with hypertension (Alter et al., 2006), but within this sample of overweight-obese youth heart rate variability measures were relatively
similar for both those with elevated SBP and normal SBP. In the current study, the groups with elevated SBP consisted of both the pre-hypertensive and hypertensive subjects and the mean SBP were not severe. In concert with our findings, Franchi and colleagues (1996) identified no differences in HRV measures when mild hypertension was present.

A limited number of studies have examined the associations between lipid levels and HRV measures. Christensen, Toft, Christensen, and Schmidt (1999) reported that HRV measures were lower in adults with dyslipidemia (high total cholesterol or high LDL-cholesterol); however, these lipid measures are not components of the Metabolic Syndrome. One adult study showed a strong \( (p < 0.001) \) linear association between HRV measures with HDL-cholesterol (Hemingway et al., 2005), which may be partially attributed to higher levels of fitness in those individuals.

Metabolic Syndrome and inflammation. The data from this study did not confirm a correlation between the Metabolic Syndrome and inflammation. There is conflicting data regarding CRP and the Metabolic Syndrome. In adult subjects, CRP and fibrinogen levels were both positively correlated with Metabolic Syndrome components (triglycerides, fasting insulin, and BMI) and negatively associated with HDL cholesterol (Ford, 2003). While the Metabolic Syndrome was associated with significantly higher levels of inflammation in adults compared to those without the Metabolic Syndrome (Kressel et al., 2008; Ridker et al., 2004), that is not always the case in child studies (Ford et al., 2005; Lambert, Delvin, et al., 2004; Weiss et al., 2004). Ford and colleagues (2005) found that CRP did correlate with the Metabolic Syndrome. In fact, among adolescents with the Metabolic Syndrome, 38.4% had a concentration of high sensitivity CRP > 3.0 mg/L. Similarly, Lambert, Delvin, and associates found a correlation between Metabolic Syndrome and CRP, which strengthened as the children aged. However, the significant association between increased CRP and clustering of the risk factors that comprise the Metabolic Syndrome became less so when insulin resistance was eliminated. Invitti and associates (2006) did not find a correlation of CRP and the Metabolic Syndrome in obese children, but they did find a correlation of uric acid (another measure of inflammation) and the Metabolic Syndrome. The use of CRP rather than high-sensitivity CRP in the current study may be one reason the Metabolic Syndrome was not associated with CRP in the current sample. Additionally, CRP values for the total group were low, attenuating potential associations.

Fibrinogen values were higher in those with insulin resistance while CRP levels were similar between the insulin resistance groups. No other Metabolic Syndrome component was associated with either CRP or fibrinogen. Anuurad and colleagues (2008) concluded that elevated levels of inflammatory markers of CRP and fibrinogen were positively associated with insulin resistance and the combination of insulin resistance and inflammation resulted in a higher degree of CAD in both Caucasians and African Americans. Similarly we found higher fibrinogen levels to be associated with insulin resistance in obese African-American youth.
Central adiposity is considered more atherogenic than other forms of obesity with adipocytes producing cytokines and inflammatory substances. The connection between obesity and elevated CRP has been observed in children (Cook et al., 2000; de Ferranti, Gauvreau, Ludwig, Newburger, & Rifai, 2006; Ford et al., 2005; Oliveira et al., 2008). Interestingly, African-American youth with central adiposity did not exhibit higher fibrinogen levels (381 vs. 356, p = 0.28) nor higher CRP levels (0.61 vs. 0.19, p = 0.09) despite the strong associations between RBMI and both CRP (r = 0.38, p = 0.001) and fibrinogen (r = 0.51, p = 0.003) found in this study. The waist circumferences cut-points chosen for this study were based on recent normative values. Further work is needed to determine whether these values correlate with other risk factors.

For the present study, elevated SBP did not correlate with CRP (0.5 vs. 0.3, p = 0.41) nor fibrinogen levels (393 vs. 348, p = 0.31). Lambert, Devin, et al. (2004) reported that the association between increased CRP values and high systolic blood pressure in school aged children was no longer statistically significant after adjustment for BMI (Lambert, Devin, et al.). In analyzing data from the National Health and Nutrition Examination Survey between 1999 and 2004, children with high-sensitivity CRP levels > 3 mg/L had higher systolic blood pressure, compared with children with levels of ≤ 3 mg/L (Lande et al., 2008). However, subset analysis revealed that the association of elevated SBP with CRP was largely limited to African-American boys. Though the subjects in the present study were all African American, two-thirds were girls. Recently, three studies examined serum uric acid was used as the inflammatory marker (Alper et al., 2005; Feig & Johnson, 2003; Jones, Richey, Alpert, & Li, 2008). Each found significant positive correlations between this inflammatory marker and blood pressure readings. The present study did not measure serum uric acid, thus comparison across studies is limited.

**Metabolic Syndrome and fitness.** In the current study of obese youth, the Metabolic Syndrome was not associated with fitness. Studies investigating the Metabolic Syndrome and fitness in children have only examined the individual components of the syndrome (Brufani et al., 2008; Franks, Ekelund, Brage, Wong, & Wareham, 2004) and/or the effects of physical activity on the various components (Giannini, Mohn, & Chiarelli, 2006; Kelly et al., 2004; Liu et al., 2006) and these investigations have yielded contradictory findings. Eisenmann and colleagues (2005) found significant correlations among low fitness and higher triglyceride and glucose levels and low HDL-levels in boys and girls with high BMI. In contrast, the current study did not find an association between any measure of the Metabolic Syndrome and fitness in obese youth. These inconsistencies in findings may be partially attributed to the varying methods of measuring physical activity and fitness, and the use of absolute values for blood pressure and lipid rather than age adjusted values employed in other studies.

There is a paucity of research regarding the contributions of physical activity or fitness to insulin resistance or impaired glucose tolerance in youth. In a group of overweight middle school children who exercised for 9 months, fasting serum glucose decreased by 48.5% (p < 0.05), whereas glucose levels increased by 10.9% (p < 0.05) in those that did not participate (Carrel et al., 2005). Wei, Gibbons, Mitchell, et al. (2000)
evaluated men with T2DM and found, physical inactivity and low cardiorespiratory fitness were independent predictors of mortality. In a study of adults with T2DM, a response to improved fitness, in combination with modest weight loss, resulted in an insulin sensitivity improvement of 59% (SD 21, p < 0.05) (Toledo et al., 2007). Further research is needed to determine if increased fitness in combination with modest weight loss, results in improved fasting glucose levels in obese youth with normal or impaired glucose tolerance.

In contrast to findings from other researchers, (Ball et al., 2004), we did not find differences in VO₂max between individuals with and without insulin resistance. While our study, like the other studies, used validated measures to calculate insulin resistance based on fasting values of insulin and glucose, we used QUICKI as the measure of insulin resistance. It is unknown whether classification of youth as insulin resistant would have changed using another method.

Allen and associates (2007) reported that VO₂max was significantly correlated with the Homeostasis Model Assessment (HOMA) of insulin resistance in middle school children, while Ball and colleagues (2004) determined that, in Hispanic children, VO₂max was negatively correlated with insulin sensitivity (r = -0.46, p < 0.05) but this relationship became non-significant once gender, Tanner stage, fat mass, and soft lean tissue mass were included as covariates (all p > 0.05). Cross-sectional studies have found that African-American children had lower insulin sensitivity and higher insulin levels than Caucasian children, as well as a lower VO₂max (Arslanian, Suprasongsin, & Janosky, 1997; Ku, Gower, Hunter, & Goran, 2000). It is presumed that the beneficial effect of improved fitness on insulin resistance reflects the combined effects of increased lean mass and reduced fat mass (Sinha, Dufour, et al., 2002). Therefore higher fit individuals should be more insulin sensitive (Weiss et al., 2004). The small sample size, high prevalence of insulin resistance, and overall poor fitness level of the subjects may have attenuated relationships among the variables in the present study.

Both overweight severity and central (abdominal) adipose distribution are associated with Metabolic Syndrome components in adults, with central adiposity, particularly visceral fat mass, considered to be more deleterious than peripheral fat mass (Howard, Ruotolo, & Robbins, 2003).

Until recently, normative measures for waist circumference in children were not available. Studies examining the relationship of central adiposity to fitness in youth were not found. Nassis et al., 2005) reported that 6-13 year olds who were obese with higher levels of fitness had less body fat than obese youth of the same BMI category who were low fit. In another study of obese children, BMI was not found to be a reliable indicator of fitness in a children (Cooper, Poage, Barstow, & Springer, 1990) suggesting that the relationship among BMI and fitness is influenced by lean muscle mass, which may be underestimated when using BMI as a measure of obesity. Further work is needed to determine whether waist circumference is associated with fitness in youth.
Population studies have indicated that fitness decreases blood pressure in hypertensive adults, but the same results are not always reported in children. While some studies have suggested that blood pressure levels are associated with levels of physical activity (Pangrazi, 2000), others have not (Calzolari et al., 1997; de Visser et al., 1994; Taylor et al., 2002). Systolic blood pressure was not associated with fitness (p = 0.80) in the present population. However, there were only mild elevations in systolic blood pressures which may have attenuated associations between the measures.

It is recognized that fitness correlates strongly with HDL cholesterol even after adjusting for BMI (Abbott et al., 1989) and physical activity improved HDL cholesterol and triglyceride levels and mortality (Blair & Brodney, 1999). However, there is a limited body of literature examining the relationship among lipids and fitness in obese youth. In a predominantly Caucasian group of 610, 9-18 years old, higher levels of fitness and habitual physical activity were associated with more favorable levels of triglycerides and cholesterol levels (Katzmarzyk et al., 1999).

The favorable lipid profile of these youth may in part have resulted from the smaller amount of body fat in those who exercised regularly as well as dietary intake of fat. The CATCH Study (Webber et al., 1996) reported that a 30-month, school-based intervention, which resulted in changes in eating behavior and physical activity did not significantly change lipids in youth. In obese youth, there may be a fitness threshold associated with favorable lipid levels that was not obtained in this group of low-fit youth. Dietary intake was not included as part of this secondary analysis and fat intake may have influenced triglyceride levels in youth.

There was no literature found regarding the Metabolic Syndrome and heart rate variability found in youth, nor did the presence or absence of the Metabolic Syndrome correlate with fitness, inflammation or heart rate variability in this population of obese African-American youth. Those with insulin resistance had higher HF values (6.22 vs. 5.96, p = 0.004), which was not expected as insulin secretion is thought to be driven by parasympathetic activation (Lustig et al., 2003) and obesity is usually associated with increased sympathetic nervous system activity. Sympathetic: parasympathetic ratios were associated with central adiposity (1.05 vs. 1.10, p = 0.02).

**Aim 4**

The fourth aim of this study was to explore the effect of age, gender and fitness on weight loss predictions in these African-American obese youth. At time 6 months, the data from 39 subjects was available for analysis. Age, gender, and severity of obesity were similar between the total sample and those in whom 6 month pre/post data was available for weight loss analysis.

There is a paucity of information regarding predictors of weight loss in overweight and obese children. Previous studies identified male gender, parental support and involvement, and compliance (Jelalinan et al, 2008), as well as previous participation.
in exercise (Reinehr, Kersting, Alexy, & Andler, 2003) as predictors of weight loss in youth. Harden et al., 2007) reported that severity of obesity and the presence of T2DM predicted weight loss with heavier adolescents losing more weight while those with T2DM were less likely to lose weight. Neither age nor gender predicted weight loss (Harden et al, 2007). In the current study, multiple regression analysis revealed that male gender and higher baseline fitness level predicted weight loss, accounting for 28% of the variance in RBMI change ($R^2 = 0.28$, model $p = 0.0028$). This finding of greater weight loss among boys is consistent with results reported by Epstein, Paluch and Raynor (2001) in which boys showed significantly better percentages of overweight changes (-15.8%) than girls (-1.0%) and had better adherence to treatment at 12-month. Additionally, boys had a propensity for physical activity which was also a significant predictor of weight loss in this study (Epstein et al., 2001).

Aim 5

The purpose of the fifth aim was to examine the relationship among the changes in RBMI, HRV, and fitness. In the current study, weight loss was significantly associated with improvements in circadian rhythmicity (SDNN) ($p = 0.004$), and there was a non-significant trend toward increased parasympathetic tone (HF) ($p = 0.07$), without changes in LF/HF ($p = 0.21$). These findings are similar to those reported by Akehi and associates (2001) who found that the rate of change in SDNN and HF correlated positively with reductions in body mass index, while changes in BMI were not associated with LF/HF changes. Consistent with findings from the current study, adult weight loss from either bariatric surgery (Nault et al., 2007) or a 3-month calorie restricted diet (Poirier et al., 2003) resulted in improvements in SDNN and parasympathetic tone, respectively. While the present study did not find significant correlations between changes in RBMI and changes in LF/HF, Endim et al. (2001) reported that adults who lost 10% to 18% of their body weight, exhibited normalization of sympathetic HRV measures and Facchini and colleagues (Facchini et al., 2003) found that even in a short term weight reduction program, which included strict calorie restrictions and intense exercise, there was a significant correlation between weight and all HRV measures. Perhaps the present study did not find significance in the changes in RBMI and LF/HF ratio because the RBMI changes were minimal and the duration of weight loss was short.

Numerous training studies support the benefits of fitness training on HRV (Gutin et al., 2000; Levy, Cerqueira, Veith, & Stratton,1992; Malfatto et al., 1996; Malfatto et al., 1998). In obese youth, Gutin and associates (2000) reported that a 4-month exercise program improved fitness, body composition, and HRV measures of parasympathetic function with greater improvements in HRV measures occurring in those with poorer pre-intervention HRV values and greater increases in vigorous physical activity. Contrary to previous studies, changes in $VO_{2\text{max}}$ were not associated with changes in HRV measures in this study of obese youth. Several factors may contribute to these results. Minimal changes in $VO_{2\text{max}}$ occurred over the 6-month intervention period. While Rossy & Thayer (1998) reported that even small differences in fitness correlated with improved HRV, others have found that correlations between fitness and HRV are only apparent in the
most fit youth (Buchheit et al., 2007). None of the youth in the current study would have been classified as “fit” based on reference values. Interestingly, Brunetto and colleagues (2005) did not find any differences in HRV measures in any fitness groups. These findings suggest that greater changes in fitness, resulting from vigorous physical activity, are needed to elicit changes in HRV measures.

There was a non-significant trend for improvements in VO_{2\text{max}} to be associated with weight loss (p = 0.07). Modest weight loss occurred in a subgroup of youth with males and those with higher baseline fitness losing more weight. Subjects were encouraged to be more physically active and free access to the YMCA was available once per week, however individuals may not have increased their physical activity during the 6-month intervention. Previous work by Goran, Fields, Hunter, Herd, and Weinsier (2000) found that there was no change in fitness level (VO_{2\text{max}}) when children lost weight. However, weight management programs employing physical activity as one component of the intervention result in concurrent weight loss and improvements in physical activity (Epstein, Paluch, Roemmich, & Beecher, 2007). These studies suggest that a change in obesity, without an increase in physical activity, does not result in an improvement in fitness level.

**Strengths and Limitations**

The lack of a uniform definition of the Metabolic Syndrome was a limitation for this study. Although the Metabolic Syndrome is a well recognized clinical phenomenon, there is no accepted definition, and the physiological changes in childhood make the definition particularly difficult to classify. Prevalence rates vary depending on the definition used to identify the syndrome, even while using the same data set (Cook, Weitzman, Auinger, Nguyen, & Dietz, 2003; Duncan et al., 2004). The differences in the many definitions found created difficulties when trying to compare results across studies and to compare the outcome in this study.

Normative values for inflammatory markers based on age and gender are not known. The values used in this study were those used in adults. There are no known studies to date which verify these values in children.

Normative values for HRV values have not been established in children and therefore can only be compared within groups. The findings in this study could also be due to a race effect as Gutin and colleagues (2005) found LF/HF was lower in African-American youth than in whites youth as did (Faulkner et al., 2003).

The definition of obesity in adults is based on body mass index (BMI), which has been correlated with morbidity and mortality. Similarly, the definition of childhood obesity is currently based on BMI; however, there are currently no data to relate morbidity and mortality to BMI values in children.
Though all subjects were obese African-American, a limitation of this study is the disparity of groups, 70% were female, and the age range was from 7.2-18.1 years. This age disparity may confound the findings as there is research that acknowledges variations in fitness response, heart rate variability change and biochemical variations of developing human and that these changes may vary according to gender, race and developmental stage. We corrected for these age and gender differences by using normative values for lipids, blood pressure, and waist circumference.

For this study a limitation was missing data. Though it is cost effective to perform secondary analysis, there was much data that was lost and therefore not available to this researcher. Waist circumference, which is a marker of central obesity, was only available for time 0 months; therefore this marker could not be evaluated for change at the 6 month mark. Fat mass was not measured. BMI and RBMI are crude measurements of obesity but changes in these measures generally involves both fat and lean body mass. It was anticipated by this study that it was the loss of fat that effected the changes in fitness, HRV and Metabolic Syndrome.

Another limitation of the study was the intrinsic problems of exercising testing. During the treadmill exercise, respiratory quotient and subject rating of perceived exertion were used to determine whether a maximal exercise test was achieved. However, fitness testing assumes maximal effort by participants and is therefore inherently biased.

**Recommendations**

Based upon the findings of this study, recommendations for research, practice and health care policy are proposed.

**Research Recommendations**

1. Replicate study with larger group of subjects with a regard for sex and Tanner stage, as well as race to determine the effect of these variables on effective weight loss, and to control for these variables which may confound findings.
2. Consider the study of aerobic exercise vs. weight training and the similarities of effects on Metabolic Syndrome components and inflammation in obese youth as aerobic exercise may be more physically awkward for extremely obese individuals to engage.
3. Consider a longitudinal study regarding inflammation, insulin resistance and development of T2DM in children. Low-grade inflammation is associated with insulin resistance and precedes the onset of type 2 diabetes mellitus in adults, but there are no comparable data in youth (Kolb & Mandrup-Poulsen, 2005).
4. Additional research on the impact of diet and exercise on inflammation in children is warranted. The rise in the prevalence of cardiometabolic risk factors in young children and adolescents, which include not only elevated triglycerides, low HDL cholesterol, but inflammatory markers such as fibrinogen and C-reactive protein has been associated with the development of chronic diseases
once only known in the adult domain. Recent research has indicated that dietary modifications such as increased intakes of antioxidants or omega-3 fatty acids or increased physical activity and physical fitness may independently modify the inflammation associated with excess adiposity in adults, but such studies were not found in children and research in this area is warranted.

5. Research has found that children are aware and concerned about their obesity (Story et al., 2001) and some are attempting weight loss on their own. Though there are many programs, research is still needed to find programs suitable in multiple settings to help all youth to develop healthful habits in nutrition and weight control.

6. The conflicting results in studies regarding fitness and heart rate variability demonstrates that more research in this area is needed.

**Clinical Practice Implications**

Obesity is a chronic disease and its treatment needs long-life follow-up. The long-term results of the obesity treatment are often disappointing and consistent prevention programs have to be considered for better results. The current study examined findings from youth participating in a weight loss program geared toward improving lifestyle behavior with education and family and child support components of the intervention. However, only small reductions in weight were achieved in a subset of individuals.

The main goal of the treatment should be to encourage the child and family to have healthy lifestyle (Epstein et al., 2007). Families who are not ready for change might benefit from counseling to improve motivation before starting treatment (Epstein et al.). In a study involving school aged children and their parents, Golan, Fainaru, & Weizman, (1998) found treatment of childhood obesity with the parents as the exclusive agents of change, induces more behavioral changes as well as greater weight loss, than the conventional approach. Though there are inherent problems with obtaining a dietary history (August et al., 2008; Caulfield, 2005), and activity information, these details are necessary for comprehensive assessment and treatment of pediatric obesity. The intervention needs to include plans to include modifications in attitudes of patients and parents, increasing physical activity and reducing energy intake (Kirk, Scott, & Daniels, 2005). The obesity treatment plan involving adolescents must consider developmental changes and the psychological characteristics of this stage of life. Additionally consideration should be given to the use of weight loss medications in adolescents as an adjunct treatment. Some providers have advocated for the use of metformin to prevent progression to T2DM in obese youth with insulin resistance or impaired glucose tolerance (Velasquez-Meyers et al., 2007).

There needs to be standardization of measurement for all markers of the Metabolic Syndrome so that treatment and research can be congruent. Although various techniques are available to measure body fat, many are impractical for clinical use. BMI was adopted as the international standard clinical measure of adiposity (de Onis, 2004), however, waist circumference should be recorded as future research may prove this measure to reflect...
fatness or morbidity better (August et al., 2008). Waist circumference standards for American children of various ethnic groups are available (Fernandez et al., 2004). Though waist circumference cut-points were not developed in children based health risks they may be an easier alternative in a busy practice to identify youth in need of weight management.

Although the prevalence of obesity in childhood has tripled since 1980 (Ogden et al., 2006), the healthcare provider community has not fully embraced this diagnosis as critical (Benson, Baer, & Kaelber, 2009). The recommended pediatric clinical practices (Barlow & Dietz, 2002) are: (1) BMI to identify overweight, (2) scheduling follow-up, (3) identification of dyslipidemia, (4) insulin resistance screening, and (5) screening for hypothyroidism in overweight patients only when clinically indicated. In a survey done in Massachusetts, awareness of these recommendations was reported by only 24.6% of the providers (Rhodes et al., 2007). When childhood obesity is identified, the advice and treatment are not consistent with current evaluation and management recommendations. In a records review, children who met criteria for obesity, were identified as such by their provider in only 53% of the time (O’Brien, Holubkov, & Reis, 2004). And in a survey of 13 pediatric practices records, only 28% of the overweight children had been identified (Dilley, Martin, Sullivan, Seshardi, & Binns, 2007). Once the child is identified, other assessments are lacking. In a recent study O’Brien and colleagues (2004) found that though 69% of the reviewed charts contained an adequate dietary history, only 15% included information regarding the child’s activity level.

While it is not feasible to conduct maximal cardiopulmonary fitness testing on all obese children, providers can elicit information on physical activity. In children, as adults, physical activity declines dramatically across age groups (Troiano et al., 2008). Physical activity “prescriptions” that target decreased sedentary behaviors, such as a reduction in screen time, or increased physical activity is associated with decreases in obesity and improved fitness (Dietz, 2001; Epstein, Paluch, Gordy, & Dorn, 2000) but providers do not consistently intervene in this manner. And, the younger the patient, the less likely it is that providers will diagnose and treat their obesity. A national survey of pediatricians, pediatric nurse practitioners, and registered dietitians revealed that, most practitioners reported that they recommended weight control for youth patients identified as obese, but only 49% intervened in cases of preschool obesity (Barlow, Trowbridge, Klish, & Dietz, 2002). Children under the age of 6 watch more than 2 hours of television at least 6 days a week (CDC, 2007), which sets the tone for decreases in physical activity. Nurses and other health care providers are positioned to provide education to families and the community regarding reducing sedentary behavior and increasing physical activity. Issuing physical activity prescriptions may be one method of emphasizing the importance of physical activity to parents and children.

Perhaps it is also time to add non-traditional assessments for the identification of those at risk for disease rising from the Metabolic Syndrome. Acanthosis nigricans may be an independent risk factor for type 2 diabetes and its detection may help providers identify those at risk (Kong et al., 2007). Not only is it important to assess obesity by height and weight calculations, the risks of consequences from childhood obesity, CVD
and diabetes, need attention too. It has been proposed for adults who are at risk for CVD to be assessed for inflammation using CRP, uric acid, fibrinogen or other markers. Data suggests that laboratory evaluations, combined with lipid levels to assist providers and patients in assessment and therefore prevention of CVD (Assmann, Schulte, & Seedorf, 2008) in adults. Thus it stands to reason that monitoring these in obese children would help providers and care givers have confidence in efforts to stave off these diseases.

While nutritional intake was not included in this analysis, Briefel and Johnson (2004) report that more than 60% of children eat too much fat and only 17% eat the recommended five or more fruits and vegetables each day (Briefel & Johnson, 2004). Obese children consume too much energy dense food and fats (Kant & Graubard, 2006; Van Horn, Obarzanek, Friedman, Gernhofer, & Barton, 2005) and in so doing have been found to have lower circulating anti-oxidants than those of normal weight (Strauss, 1999). Supplements of these anti-oxidants have been recommended for adults at risk for CVD, accordingly perhaps it’s time to recommend these to obese children too.

**Policy Implications**

Childhood obesity which has quadrupled in the last 40 years leads to devastating and costly adult disease (Anderson, 2004; Anderson & Butcher, 2006; Chartier, 2004). Nurses have an influential clinical role to play in its prevention through public advocacy and direct care of children and families. Dey, Schiller, & Tai, (2004) found that 74.5% of children under the age of 18 were seen by a health care professional during a six month period which provides a great opportunity for nurses and nurse practitioners to measure and track BMI or waist circumference, and counsel children and their parents regarding preventive measures. In 1994, an expert committee determined that body mass index (BMI) should be used routinely to screen for overweight adolescents. However other research suggests waist circumference maybe an easier and valid method of assessment. While not all states have instituted obesity screenings at school, it is feasible to implement these screenings and provide families with a reference for comparison of their child’s weight.

Further, school nurses should be supported in efforts to promote awareness and prevention of childhood obesity. A survey of school health nurses in Minnesota (Kubik, Story, & Davey, 2007) found 76% agreed health services used for obesity prevention was a good idea and that obesity prevention tasks in this group increased as perceived support for school-based obesity prevention from health care providers and school administrators, teachers and foodservice staff increased. The school environment can also work as a change agent in prevention of childhood obesity by deliberately instituting interdisciplinary curriculum programs in the school curriculum such as Jump-in , for 4th, thru 6th graders; Planet Health (Gortmaker et al., 1999; Hernandez et al., 1999), an for sixth through eighth grade students and SPARK (Sallis et al., 1993; Williams et al., 1998) for preschoolers.
Recent studies (Koutedakis, Bouziotas, Flouris, & Nelson, 2005; Sur et al., 2005) indicate that the positive energy balance which causes overweight in childhood is not due to increased energy or fat intake, but rather to a decreased energy expenditure. This is a confirmation of two met analysis reported by (Maril et al., 2004; Marshall et al., 2004), that over the school age years, a consistent decline in physical activity is seen, with males decreasing about 2.7% per year and females decreasing about 7.4% per year. These data suggest that older youth and females are at increased risk of obesity because of a sedentary lifestyle. This trend was confirmed by (Wang & Zhang, 2006) who found American children at lower socio-economic levels were at greater risk. In the current study of obese African-American youth, overall fitness was poor. Taken together, these findings valid the importance of physical activity and education in public schools, and lend support for re-instatement of physical activity into the school curriculum through the high school years.

Theoretical Implications

The conceptual model for this study identified a relationship among variables and that these variables were interdependent. The Metabolic Syndrome, or the components of the syndrome, is not only a precursor to cardiovascular disease and diabetes; it was theorized that the Metabolic Syndrome was also related to autonomic dysfunction and therefore contributed to decreases in HRV. Additionally low fitness was theorized as affecting the Metabolic Syndrome, as well as inflammation and heart rate variability.

Findings from the current study support the proposed relationship among fitness, HRV, and fibrinogen. However, Metabolic Syndrome was not significantly associated with fitness, HRV, or inflammation. Metabolic Syndrome components of insulin resistance and central adiposity were associated with HRV measures, while HDL-cholesterol was associated with fibrinogen. Given that higher fitness is linked to higher HDL-cholesterol levels, this relationship may be reflective of fitness levels. The severity of obesity and poor fitness levels of subjects may have attenuated relationships among variables.

It was theorized that weight loss would positively affect Metabolic Syndrome, HRV, inflammation, and fitness levels. However, data at the 6-month time point was not available for all variables. The relationship between changes in RBMI, fitness (VO\textsubscript{2max}), and HRV were explored. Weight loss resulted in improved HRV measures of SDNN, and there was a trend toward higher parasympathetic measures of HRV and improved fitness, despite only modest weight reductions occurring in a subset of individuals. These findings support the theoretical model depicting weight loss as improving fitness and HRV in obese youth.
LIST OF REFERENCES


WHO and ATPIII proposals for the definition of the metabolic syndrome in 


Relationships between media use, body fatness and physical activity in children 


rythm of heart rate and heart rate variability. *Archives of Disease in Childhood, 83*(2), 179-182.

rate variability in children with congenital heart disease. *European Journal of 
Pediatrics, 157*(12), 967-971.

*American Family Physician, 58*(6), 1360-1365.

Prevalence of insulin resistance and associated cardiovascular disease risk factors 
among normal weight, overweight, and obese individuals. *Metabolism: Clinical 

(2002). Differentiation between obesity and insulin resistance in the association 
with C-reactive protein. *Circulation, 106*(23), 2908-2912.

C., Jr. (2006). Pathobiological determinants of atherosclerosis in youth risk scores 
are associated with early and advanced atherosclerosis. *Pediatrics, 118*(4), 1447- 
1455.

(2002). A school-based intervention can reduce body fat and blood pressure in 

validation of the SHAPEDOWN program. *Journal of the American Dietetic 
Association, 87*(3), 333-338.

Improvement of early vascular changes and cardiovascular risk factors in obese 
children after a six-month exercise program. *Journal of the American College of 
Cardiology, 48*(9), 1865-1870.

metabolic syndrome on heart rate variability: Using the NCEP-ATP III and IDF 


Belinda J. Fleming was born May 26, 1953, in Houston, Texas. She earned a BS in Nursing from Southern Adventist University in Collegedale, Tennessee, in 1976. While teaching in Methodist Hospital School of Nursing in Memphis, Tennessee, she completed her MSN from the University of Tennessee Health Science Center, Memphis, Tennessee, in 1987. Belinda began her career as a family nurse practitioner in 1985 and has worked in a variety of settings in that capacity, including inner-city and rural clinics, emergency departments, school-based clinics, private practice and military installations while continuing to teach at Union University, the University of Memphis, and the University of Tennessee Health Science Center as well as serving in the United States Navy Reserve. Currently, she is an assistant professor of nursing at the University of Tennessee Health Science Center, Memphis, Tennessee, and a family nurse practitioner in private practice. She will receive the Doctor of Philosophy degree in May, 2009.