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Improving Metabolic Health in Adult, Premenopausal, Overweight Women through Moderate Intensity Intermittent Exercise

The prevalence of *obesity* in the United States has reached epidemic proportions, effecting over 78 million adults and 12.5 million children and adolescents in the United States during 2009-2010 (Ogden, Carroll, Kit, & Flegal, 2012). Associations between obesity and metabolic disease are strongly supported in current literature and reversing their prevalence remains a national priority (U. S. Department of Health and Human Services, 2013). Though exercise is recognized as one important component in the treatment of these conditions, there has not been a clear consensus on what is the most effective intensity for increasing metabolic health in this population.

Chapter 1. Introduction

Obesity is associated with increased risk of cardiac disease, respiratory and endocrine dysfunction, liver and gallbladder diseases, malignancies, psychological diseases and losses of orthopedic function (Mitchell, Catenacci, Wyatt, & Hill, 2011; Rotondi, Magri, & Chiovato, 2011; Schelbert, 2009; Schindler et al., 2006). These conditions have been attributed to metabolic derangements that frequently accompany obesity.

Problem

Overweight and obesity prevalence.

Data obtained during the 2009-2010 National Health and Nutrition Examination Survey (NHANES) indicated that 69% of the adult U. S. population met clinical diagnostic criteria for diagnosis of *overweight* or obese conditions (68.8% age adjusted prevalence, 95% CI [65.9%-71.5%]). Overall, men had a higher combined prevalence of being overweight and obese than women (73.9%, 63.7%, respectively). When males were compared across ethnic and racial categories, White males had the lowest prevalence of obesity (36.2%) and Black males the highest (38.8%). The trend for females was more concerning: the prevalence of overweight and obese Hispanic (41.4%), Mexican American (44.9%) and Black women (58.5%) were all considerably higher than White females (32.2%) or their male counterparts. The genders peak prevalence occurred during different times; men peaked between 40 and 59 years (37.2%) while for women it was after 60 years (42.3%) (Flegal, Carroll, Kit, & Ogden, 2012, p. 493).

The NHANES data were obtained with field surveys and exams. The National Health Interview Survey (NHIS) conducted from January 2012 through September 2012 estimated a significantly lower prevalence of overall obesity adjusted for age – 28.8%. Even though the prevalence numbers were significantly lower than those calculated by Flegal et al. (2012), the trends were remarkably similar between the two surveys and one explanation may be the measure used by the NHIS, which relied on self-reported height and weight values and the exclusion of approximately 6% of the responses received for “unknown values” (Ward, Schiller, Freeman, & Peregoy, 2013).

Obesity and the metabolic syndrome.

Hypertension, insulin resistance, hypertriglyceridemia, decreased high density lipoproteins (HDL), hyperglycemia, increased waist size secondary to central adiposity and proinflammatory and prothrombic states are classic risk factors defining the *metabolic syndrome* (MetS; Grundy et al., 2005; McCullough, 2011). Strongly associated with obesity, the MetS effects an estimated 38.5% of the population in the U. S. and has the highest prevalence rate in men and women whose cardiorespiratory fitness is in the lower third (Ford, Li, & Zhao, 2010; Lamonte et al., 2005). Among 41,474 asymptomatic patients, the overall prevalence rate was 20.5%, associated with increasing age (6.6% age 18-29 years, 34.6% age 70 years and older), sex (males greater than females age less than 50, females greater than males age greater than 49) and ethnicity (Whites with the highest overall rate, 21.8%; Hispanic and Mexican American with the highest age associated increase, 6.3% age 18-29 years to 36.5% age 70 years or greater) (Sumner, Sardi, & Reed, 2012).

Physical activity and sedentary lifestyle.

Regular moderate intensity *physical activity* (PA) is associated with increased metabolic health. Sedentary individuals experienced increased all-cause mortality and cardiac risk due to their lower cardiorespiratory fitness and the development of metabolic disturbances, including elevated levels of visceral and abdominal fat, decreased insulin sensitivity, dyslipidemia with decreased particle size of low-density lipoprotein cholesterol (LDL), and increases in total LDL and triglycerides (Matthews et al., 2012; Grundy et al., 2005; Slentz et al., 2005). A sedentary lifestyle significantly increases the individual risk of developing the MetS (odds ratio (OR), 1.61, $p = 0.04$, 95% CI [0.97, 2.67]; Bankoski et al., 2011).

The current minimum exercise frequency recommendation for adults in the U.S. is 30 minutes of daily PA at a moderate intensity, five times per week for maintenance of health (Garber et al., 2011). Less than one half of adults in the United States currently achieve this recommendation (47.8%, 95% CI [46.10%, 49.49%]), a number that declines as age increases, starting with the group aged 25-64 years. Hispanic (38.8%) and Black (41.1%) adults meet recommended PA goals less than White adults (51.9%) and in all age groups, women fail to meet the PA goals more than males (Ward, Schiller, & Freeman, 2013).

Research Focus

The metabolic benefits of regular aerobic PA can attenuate the increasing prevalence of the MetS and obesity in society. Current research in the Human Performance Lab at Southern Adventist University (SAU) is investigating which type (continuous or intermittent) and intensity (high or moderate) of physical activity best improves *metabolic health measures* (MHM) within the vulnerable population of obese or overweight adult females.

Definitions of Terms

Body Mass Index (BMI): Calculated value that describes relative weight for height and significantly correlated with total body fat content (kg / m^2; U. S. Department of Health and Human Services, 1998, p. xiv).

Continuous Exercise (SSE): Exercise activity intensity remains constant for the duration of one single session (Garber, 2011, p. 1341).

Fat Free Mass (FFM): Combined weights of essential lipids, water, proteins, minerals, glycogen and residual elements; synonymous with "lean body mass" (Wang, Pierson, & Heymsfield, 1992, p. 21)

Heart Rate, Maximum (HR_{max}): Maximum physiological HR; Obtained during a valid maximal exercise test, calculated from submaximal testing with the modified Astrand – Ryhming nomogram (Astrand & Ryhming, 1954; Pescatello, Arena, Riebe, & Thompson, 2014, p. 81) or predicted from age (220 – age, years; Pinkstaff, Peberdy, Kontos, Finucane, & Arena, 2010; Pescatello et al., 2014).

Heart Rate, Reserve ($HR_{reserve}$): Calculated value obtained by subtracting the HR_{rest} from HR_{max}.

Heart Rate, Rest (HR_{rest}): Measured value of resting heart rate.

High Intensity Exercise (HIE): Physical activity between 64% and 90% of VO_{2max} that is planned and repetitive with the intention to achieve physical fitness; also known as vigorous intensity. For this paper, the subcategories of "near maximal" and "maximal" intensity (greater than 91%) are included (Garber, 2011, p. 1341).

Intermittent Exercise (IT): Exercise activity intensity is varied during one single session (Garber, 2011, p. 1340).

Low Intensity Exercise (LIE): Physical activity between 37% and 45% of VO_{2max} that is planned and repetitive with the intention to achieve physical fitness; also known as light intensity (Garber, 2011, p. 1341).

Metabolic Equivalent of Task (MET): Measure of energy cost of physical activities and equal to 1 kcal $\cdot$ $kg^{-1} \cdot h^{-1}$ or a resting metabolic rate (RMR) of 3.5 $mL^{-1} \cdot kg^{-1} \cdot min^{-1}$. One MET is the equivalent energy expended by an individual at rest (Ainsworth et al., 2011).

Metabolic Health Measures (MHM): Measured anthropometric and laboratory values within the following categories: Adiposity, lipoprotein profile, cardiorespiratory fitness, glycemic regulation, systemic inflammation and endocrine and metabolic fitness (Appendix A).

Metabolic Syndrome (MetS): A pattern of interrelated metabolic risk factors that promote atherosclerotic cardiovascular disease (Grundy et al., 2005, p. 2735).

Moderate Intensity Exercise (MIE): Physical activity between 46% and 63% of VO_{2max} that is planned and repetitive with the intention to achieve physical fitness and health (Garber, 2011, p. 1337).

Obesity: Body mass index equal to 30.0 or greater (U. S. Department of Health and Human Services, 1998, p. xiv).

Overweight: Body mass index equal to 25.0 and less than 30.0 (U. S. Department of Health and Human Services, 1998, p. xiv).

Physical Activity (PA): "'Any body movement produced by skeletal muscles that result in energy expenditure'… above resting (basal) levels. Physical activity broadly encompasses exercise, sports and physical activities done as part of daily living, occupation, leisure and active transportation" (Garber, 2011, p. 1337).

Respiratory Exchange Ratio (RER): Ratio of carbon dioxide exhaled to oxygen inhaled in one breath. Used to estimate the respiratory quotient (RQ).

Respiratory Quotient (RQ): Carbon dioxide eliminated divided by oxygen consumed. This number will range from 0.7 (complete fat burning metabolism) to 1.0 (complete carbohydrate burning metabolism).

VO_{2max}: Maximal oxygen uptake; maximum ability of the body to transport and utilize oxygen (Garber, 2011, p. 1339).

VO_{2peak}: Highest oxygen uptake value obtained during testing which may be less than VO_{2max}.

Theoretical Framework

Health promotion has been defined as behavior that is motivated by a person's desire to improve well-being and health to the greatest degree possible (Pender, Murdaugh, & Parsons, 2006). *Disease prevention* is motivated by the desire to avoid further illness and maintain function within the constraints of a person's illness. Sedentary, overweight female participants are likely to have some degree of metabolic disease present. Therefore, the goal of improving metabolic health through exercise is best described as a health promoting activity. The health belief model (HBM; Rosenstock, Strecher, & Becker, 1988), focuses on disease-prevention through avoidance is not as well matched as other theories for formulating the underlying theoretical constructs in this instance. Social cognitive theory (SCT; Bandura, 1986; Bandura 2004), the transtheoretical model (TTM; Prochaska, DiClemente, and Norcross, 1992) or the health promotion model (revised) (HPM-r; Pender, 1996), have all been used successfully in prior studies in forming conceptual frameworks for exercise and health promotion (Robbins et al., 2001; Wood, 2008).

Exercise behavior is significantly associated with *Perceived self-efficacy* (PSE; Wood, 2008). Perceived self-efficacy is the personal perceived ability to successfully complete a course of action and is developed through experiences where the action is mastered, learning from observation of others experiences, verbal persuasion, and somatic feelings (Bandura, 1977). All three frameworks (SCT, TTM, HPM-r) include PSE into their theory.

The health promotion model is the conceptual framework for this review. The model expands the central premises of SCT and describes individual health promotion with a more holistic approach, including personal physiological, behavioral, interpersonal and situational influences with prior behavior, self-efficacy and activity-related affects, perceived benefits and barriers to action and commitment to a plan of action (Pender, Murdaugh, & Parsons, 2006). Further research to study associations between physical activity in overweight and obese women and the variables of self-efficacy and activity-related affects is needed.

Purpose Statement

In overweight and obese, premenopausal adult females, what effect does a program of either continuous moderate intensity walking, intermittent moderate intensity walking or intermittent high intensity walking have on participants' metabolic health as measured by changes in RER, VO_{2max} and FFM.

Chapter 2. Literature Review

General Literature

Concepts of Exercise Physiology.

Aerobic and anaerobic cellular metabolism.

Energy produced.

Energy for cellular activities requires formation of adenosine triphosphate (ATP) which is produced through either anaerobic or aerobic metabolic pathways. These produce a net total of two or 38 ATP, respectively. There is a significant difference in the amount of ATP produced depending on which substrate is oxidized. Glucose produces two substrates, which produce a net amount of 38 ATP while fatty acids yield a net gain of 146 ATP per molecule (Guyton & Hall, 1996).

Anaerobic cellular respiration.

Glycolysis is the anaerobic pathway that occurs in the cytoplasm of the cell and leads to the breakdown of a glucose molecule into two *pyruvic acid* molecules and free hydrogen ions. The free hydrogen ions combine with *nicotinamide adenine dinucleotide* (NAD) to form NADH. This inefficient process releases only about 3% of the glucose molecule's available energy and results in the net production of two ATP (Guyton & Hall, 1996).

Without oxygen available to drive the aerobic reactions, the end products are converted to *lactic acid* through the *fermentation* process. Lactic acid is strongly associated with exercise fatigue and muscle cramping. This process is reversible once oxygen is available to the cells (Guyton & Hall, 1996).

Aerobic cellular respiration.

The aerobic pathway takes place in the mitochondria and only occurs when oxygen is available to the cell. When completely oxidized, one mole of glucose yields 686,000 calories of energy, while the same amount of fatty acids will yield more than double that number. Along with ATP, this process produces the waste products of carbon dioxide (CO_2) and water (H_2O). This system is 66% efficient; the remaining 34% of energy is released as heat (Guyton & Hall, 1996).

Measures of metabolic fitness.

Metabolic substrate utilization.

The *respiratory exchange ratio* (RER) is obtained from the ratio of the amount of CO_2 exhaled divided by the amount of oxygen (O_2) inhaled. Values typically range from 0.70- 1.0, indicating that the majority of substrates used for cellular respiration are either fats or carbohydrates, respectively and are used to estimate the *respiratory quotient* (RQ; Brockway, 1987).

Aerobic fitness.

Aerobic cardiopulmonary fitness is determined by the measurement of the maximal oxygen uptake (VO_{2max}). Conceptually, this measurement relies on the *Fick principle*, which states that the amount of a particular marker uptake in the organ is equal to the amount of the marker in arterial blood to the organ less the amount of marker found in the venous blood from the organ (Fick, 1870; Tichauer & McCoy, 2012). This relationship is described by the equation $VO_2 = Q \cdot [C_A\text{-}C_V]$, where VO_2 is the rate of oxygen uptake, Q is the rate of blood flow or cardiac output (stroke volume x heart rate), C_A is the arterial oxygen concentration and C_V is the venous oxygen concentration (Fritts Jr., & Courand, 1958; Pescatello, Arena, Riebe, & Thompson, 2014).

Physical Activity.

Exercise training improves both fitness and metabolic health measures; however fitness is not necessarily a synonym for health. Moderate intensity PA is associated with a lower risk of upper respiratory infections, while high intensity PA is associated with a higher risk (Nieman, 1994). Weight lifters have been found to develop similar cardiac physiological profiles as those patients with hypertrophic cardiomyopathy (Anastasakis et al., 2005). Specifically, a divergence of health and fitness indices in overweight and obese women has been found to be related to the intensity of their PA (Mayer, Beihl, White, Blair, & Martin, 2012).

Exposure to regular moderate and high levels of occupational and leisure-time PA has been associated with a decreased hazard ratio of myocardial infarction in women (0.84 and 0.82, 95% CI [0.44-1.63] and [0.49-1.40], respectively) and with a significantly decreased hazard of "definite fatal cardiac disease" in both men and women (0.66 and 0.50, $p < 0.001$, 95% CI [0.48-0.92] and [0.37-0.68], respectively; Fraser, Strahan, Sabaté, Beeson & Kissinger, 1992). Lower risks of myocardial infarction were noted with light to moderate occupational PA (odds ratio (OR), 0.78 CI [0.71-0.86] and 0.89 CI [0.80-0.99], respectively) and increasing the amount of time spent weekly in exercise from 30 minutes to greater than 210 minutes (OR 0.92, CI [0.67–1.28], OR 0.71, CI [0.63–0.79], respectively; Held et al., 2012).

An inverse association between levels of PA and ischemic stroke in middle-aged women has been found. When walking PA was further analyzed, the relative risks of ischemic stroke decreased significantly with increases in intensity (Moderate 2-2.9mph, RR, 0.71, $p < 0.001$, 95% CI [0.53-0.96]; Brisk ≥ 3mph, RR, 0.47, $p < 0.001$, 95% CI [0.31-0.68]) and doses (Hu et al., 2000).

Intensities of exercise PA have been described as low, moderate, and high and can be performed *continuously* (SSE) or *intermittently* (IT). *Low intensity exercise* (LIE), is defined as exertion intensity between 37% to 45% of maximal oxygen consumption (VO_{2max}). It is reported to provide little aerobic or cardiorespiratory fitness benefit, but is traditionally well tolerated and promotes range of movement (Garber et al., 2011).

Moderate intensity exercise (MIE), (46% and 63% VO_{2max}) is associated with maximal fat oxidation, a lowering of very low density lipoproteins (VLDL) and triglycerides. It is also associated with increased mitochondrial biogenesis, inhibition of platelet aggregation and vascular endothelial growth factor and capillary growth within skeletal muscle (Achten, Gleeson, & Jeukendrup, 2001; Garber et al., 2011; Hoier, Passos, Bangsbo, & Hellsten, 2013; Rauramaa et al., 1986; Thomas et al., 2010).

High intensity exercise (HIE) or vigorous intensity (64% VO_{2max} through 90%) is associated with reductions of visceral and central fat, with increases in *fat free mass* (FFM) and aerobic power. Additionally, improvements in arterial stiffness, increased levels of HDL-C and insulin sensitivity are noted with HIE (Ciolac, 2012; Heydari, Freund, & Boutcher, 2012; Garber et al., 2011; Swain & Franklin, 2006; Trapp, Chisholm, Freund, & Boutcher, 2008).

Obesity.

In the past four decades, there has been an average of a 400 kilocalories per day positive caloric difference between energy consumed and energy expended (Swinburn et al., 2009). While the causes of the current obesity epidemic continue to be debated, scientists agree that PA is necessary for maintaining metabolic health. Physical activity has decreased with less than half of adults meeting recommended daily goals (Ward, Schiller, & Freeman, 2013). An inverse relationship between an individual's BMI and physical activity intentions has been observed (R = .12, F (1, 1060) = 14.55, $p < 0.00$, $\beta = -.12$, $p < 0.00$; Caperchione, Duncan, Mummery, Steele, & Schofield, 2008) supporting the findings of Ball, Crawford and Owen (2000) that obesity was an obstacle to physical activity.

The current recommendation of 150 minutes of moderate intensity PA weekly provide metabolic health benefits, but fail to provide enough additional energy expenditure for significant weight loss. Achieving a safe weight loss goal of one to two pounds per week requires a daily energy deficit of 1255 – 2092 kilojoules (kJ; 300-500 kilocalories, kcal) for a persons with a *body mass index* (BMI) between 27 and 35, and a deficit of 2092 – 4184 kJ (500-1000 kcal) for those with a BMI above 35 (Okay, Jackson, Marcinkiewicz, & Papino, 2009). These values are consistent with findings during a 30 month follow-up that persons expending more than 10460 kJ (2500 kcal) per week demonstrated greater weight loss and regained less than those who expended less (Tate, Jeffery, Sherwood, & Wing, 2007).

As discussed in previous sections, an obese and overweight population is associated with additional personal health burdens which collectively impact society. Many of these burdens result from metabolic dysfunction, most notably the MetS, which is strongly associated with obesity, hyperlipidemia, fatty liver disease, glucose intolerance and hypertension (Kogiso, Moriyoshi, & Nagahara, 2007) and has been implicated in the development of type 2 diabetes (T2DM), atherosclerotic cardiovascular disease (ACVD) and nonalcoholic fatty liver disease (NAFLD) (Cerezo, Segura, Praga & Ruilope, 2013). Exercise modalities for obese individuals appear to be more appropriate when focused on achieving metabolic fitness rather than weight control (Blackburn, Wollner, & Heymsfield, 2010).

Research Literature

Exercise motivation and behavior.

Exercise motivation is challenging to study, with numerous psychological, social and behavioral factors identified. The Transtheoretical Model (TTM; Prochaska, DiClemente, and Norcross, 1992) of behavior change describes five stages of change of individual behavior participation and has been validated in adults for exercise behaviors (Marcus, Rossi, Selby, Niaura, & Abrams, 1992; Prochaska et al., 1994; Marcus, King, Clark, Pinto, & Bock, 1996; Reed, Velicer, Prochaska, Rossi, & Marcus, 1997). The TTM has been validated in an overweight and obese population (*N* = 670, age mean 50.9 years, female 53.3%, white ethnicity 92.6%, BMI mean 30.6) for moderate exercise (Sarkin, Johnson, Prochaska, & Prochaska, 2001).

Intrinsic and extrinsic motivation behaviors during moderate exercise have been found to change depending on the TTM stage. The extrinsic and intrinsic motivation scores increased from the lowest stage (contemplation) to the highest one (maintenance). When the subscales were standardized, extrinsic motivation in the form of “tangible rewards” was significantly greater than the extrinsic motivation of “competition-social” and two intrinsic motivation subscales, “effort-competence” and “interest-enjoyment” during the contemplation and preparation phases ($p < 0.008$; Buckworth, Lee, Regan, Schneider, & DiClemente, 2007, p. 450-451).

Self-efficacy as described in social cognitive theory (SCT) and the TTM has been found to significantly predict weight change from the levels of exercise behavior of obese and overweight women (SCT, $R^2 = -.23$, $p = 0.013$, TTM, $R^2 = -.26$, $p = 0.010$; Palmeira et al., 2007). Exercise self-efficacy and intrinsic exercise motivation were important components for successful long-term weight loss in overweight and obese women ($R^2 = .17$, $P < 0.001$, effect ratio: 0.89; Teixeira et al., 2010). Weekly meetings addressing common barriers to exercise among obese women significantly improved self-efficacy scores from baseline values at 24 weeks and 48 weeks (1.22 ± 0.14, 1.67 ± 0.16, $p = 0.016$, 1.91 ± 0.17, $p < 0.05$, respectively; Dallow & Anderson, 2003).

Moderate intensity exercise has been found to be more accepted by sedentary individuals than vigorous exercise. These sedentary individuals may need to start at lower intensities (ACSM Evidence Category B) and benefit from the prescription of short bouts (less than 10 minutes each; ACSM Evidence Category B) to remain motivated (Garber et al., 2011).

Exercise attrition and protocol adherence.

Sedentary individuals typically experience many challenges and barriers to exercise and leisure-time PA which can be troublesome to researchers when they design exercise studies. Participant attrition in these studies is typically 25-50 % and adherence to intervention protocols averages 66% (Linke, Gallo, & Norman, 2011).

In a systematic literature review examining 14 studies with the goal of determining exercise attrition and adherence rates of intermittent versus sustained aerobic exercise interventions in sedentary adult populations, reviewers were hindered by the lack of consistent definitions for reporting adherence or attrition in the studies. Attrition rates were between 7-58% and not significantly different between groups with sustained exercise protocols and groups with short bout, intermittent protocols. High attrition studies were associated with longer duration protocols and the absence of any interventions directed towards behavioral changes. Studies with relatively short intervention durations, eight to 20 weeks, and having behavioral interventions were associated with greater levels of participant completion (Linke, Gallo, & Norman, 2011).

Exercise and metabolism.

Sedentary conditions and metabolism.

Physical activity is necessary for maintenance of metabolic health. In one RCT of sedentary individuals, subjects developed significant metabolic dysfunctions in as little as six months of inactivity when compared to low amount MIE, low amount HIE and high amount HIE. These included increased visceral fat (8.6%, $p = 0.001$, 1.7%, $p = 0.58$, 2.5%, $p = 0.43$, -6.9%, $p = 0.038$, respectively) and abdominal fat (3.9%, $p = 0.015$, 0.2%, $p = 0.91$, 2.0%, $p = 0.38$, -6.8%, $p = 0.001$, respectively; Slentz et al., 2005). Sedentary individuals exhibited worsening lipoprotein profiles, glycemic regulation, and cardiorespiratory fitness as evidenced by increased levels of LDL-C and small LDL particles, elevated FBG and decreased insulin sensitivity and RMR and diminished cardiorespiratory fitness markers after six months of inactivity (Patel, Slentz, & Kraus, 2011).

Exercise and energy expenditure.

Four variables determine a person's total daily energy expenditure: The sleeping energy expended, the energy of arousal, a thermic effect of food and the cost of physical activity. The first two determine the total resting energy expenditure (REE), which is estimated fairly accurately by determining a person's RMR. It is reasonable to expect that increasing a subject's REE would result in weight loss (Ravussin & Bogardus, 1989).

Imposing caloric restrictions reduces the RMR, leading to limited weight loss as the body self-regulates metabolism to compensate. Researchers have hypothesized that vigorous exercise would result in an increased RMR. There are conflicting reports of changes in RMR with exercise and caloric restriction. Donahoe, Lin, Kirschenbaum and Keesey (1984) found that the expected dietary depression of RMR was attenuated by vigorous aerobic exercise (30 minutes at 80% HR_{max}, four times weekly). In contrast, researchers failed to find any evidence that resting energy expenditure (REE) returned to beginning values in obese women prescribed a controlled dietary intake and a vigorous aerobic exercise program (30 minutes at 70% VO_{2max}, 5 times weekly; Henson, Poole, Donahoe, & Heber, 1987). Another study supports these findings after demonstrating that PA did not significantly change RMR after a one year moderate intensity (60% HRR) exercise intervention among untrained adults (N=17, 7 male, 10 female, 42 ± 5 years, 24.6 ± 2.2 BMI; Scharhag-Rosenberger, Meyer, Walitzek & Kindermann, 2010).

Lipoproteins and exercise.

Elevated levels of very low density lipoproteins, rich in Triacylglycerol (TAG), have been implicated as risk factors in coronary health disease and atherosclerosis. Normally measured as fasting values, researchers have found that these lipoproteins are catabolized during the postprandial state. Most individuals spend the majority of time in this state and reduction of TAG lipoproteins during this period is considered essential. A literature review by Miyashita, Burns, and Stensel (2013) found that postprandial TAG lipoproteins could be lowered 12-27 % with exercise. Middle-aged men with the MetS lowered their TAG 27% with long duration (100 minutes) walking exercise at intensities of 35-45% VO_{2max}. Inactive adults aged 34-66 years lowered their TAG 12 % when walking at 60% VO_{2max} in either one 30 minute session or three 10 minute sessions.

Thomas et al (2010) used a two phased intervention to study the effects of weight regain on metabolic markers in overweight or obese adults with MetS. After completing phase I, a combined caloric restriction and moderate intensity exercise program for 4-6 months, the subjects regained 50% of their weight loss during phase II through controlled protocols, randomized into exercise and no-exercise groups. A significant ($p < 0.05$) improvement in "almost all parameters assessed [blood pressure, regional fat, glucose, lipids, and inflammatory markers]" was noted after phase I (p. 3). Following phase II, the exercise group preserved their metabolic marker gains of phase I with the exception of worsening triglycerides, lipoprotein cholesterols and abdominal adiposity. There was no breakdown of individual numbers, significance levels or confidence intervals given.

In their randomized clinical trial, Kraus et al. (2002) studied the effects of exercise intensity and amount on lipoproteins in 111 sedentary, overweight adults over eight months. Using three treatment arms (low amount – moderate intensity, low amount – high intensity, and high amount – high intensity) with a non-exercise control, the researchers concluded that it was the amount, not intensity, of exercise that improved metabolic lipoprotein markers.

This conclusion was further supported by Slentz et al (2004). Additionally, they found that their data described a "dose-response effect" for amount of exercise and fat mass loss (p. 39). Independent of intensity, the researchers estimated that approximately six to seven miles per week of exercise was needed to maintain current weight in their subjects (N = 120, 55 females, 45 males, 52.8 ± 6.4 years, 29.7 ± 3.2 BMI, 2122 ± 649 kcal/d, 48.8 ± 10.3 % CHO, 33.8 ± 8.4 % fat, 15.8 ± 5.4 % protein).

In contrast, a six month, three treatment arm RCT of sedentary, overweight or obese, postmenopausal women (N = 464, 57.3 ± 6.4 years, 31.8 ± 3.8 BMI, 2238 ± 973 kcal/d, 28.8 ± 4.8 % body fat, 118.3 ± 26.3 LDL-C, 57.4 ± 14.6 HDL-C, 129.5 ± 63.4 triglycerides, baseline values) exercising at 50% VO_{2peak} did not find any significant changes in weight, body fat %, LDL-C, HDL-C, or triglycerides. While this study's treatment arms varied the amounts of energy expended (4, 8, 12 kcal/kg), researchers had a limited exclusion criteria and did not control dietary behaviors, exclude smokers or medication use of cholesterol, thyroid, blood pressure or antidepressants. The authors specifically note a lack of treatment versus baseline hormone use interaction, but make no mention of possible interactions with the other metabolic confounders (Church, Earnest, Skinner, & Blair, 2007).

***The metabolic syndrome and exercise*.**

The MetS is characterized by the presence of three or more of the following risk factors: the lipid disorders of hypertriglyceridemia, and hypoalphalipoproteinemia (low HDL-C), impaired fasting glucose, hypertension and increased waist circumference (ATP III scores; U.S. Department of Health and Human Services, 2002). Over a period of nine years, Bradshaw, Monda, and Stevens (2013) noted that light and moderate intensity levels of physical activity (2-2.75, 2.75-5 MET·hrs/week, respectively) have an inverse association with the risk of developing the MetS in normal, overweight and obese middle-aged subjects (*n*=9,203, HR light 1.03, 0.97, 1.07 and moderate 0.71, 0.84, 1.06, respectively, 95% CI [light 0.87, 1.23; 0.87, 1.09; 0.92, 1.24; moderate 0.58, 0.86; 0.75, 0.95; 0.90, 1.25, respectively], $p = 0.02$). Interestingly while low amounts of moderate intensity ($n = 50$, 40-55% VO_{2peak}, 179±37 minutes/week, 3.5±0.6 sessions/week) and high amounts of vigorous intensity exercise intensity ($n = 61$, 65-80% VO_{2peak}, 175±36 minutes/week, 3.7±0.7 sessions/week) significantly lowered ATP III scores in middle-aged adults from baseline values (mean and *SD*, -0.5±1.1, $p < 0.01$, -0.5±1.1, $p < 0.01$, respectively), low amounts of vigorous intensity exercise did not ($n = 45$, 68-80% VO_{2peak}, 114±29 minutes/week, 3.0±0.5 sessions/week, -0.2±1.1, non-significant; Johnson et al., 2007).

Exercise intensity.

Previous research in exercise intensity has attempted to determine which type provides the most beneficial physiological changes. Systematic review of available studies is hindered because most studies fail to ensure equal total energy expended between moderate and vigorous treatment arms. Distance based physical activity objectives offer more accurate measurements of total energy expenditure and better health benefits when used for exercise prescriptions (Williams, 2012).

Energy substrate oxidation and exercise intensity.

Exercising at the optimum intensity for individual fat oxidation is a challenging goal. Aerobic exercise at low to moderate intensity has been found to be the most efficient for fat substrate metabolism. The peak intensity depends on the individual's aerobic fitness and ranges from 33 – 65% VO_{2max}. While one group of 18 normal weight, trained male cyclists had maximum fat oxidation at 64±4% VO_{2max} (74±3% HR_{max}), when overweight men and women were studied, women had significantly greater fat oxidation rates at 30% VO_{2max} then men (p = 0.04) and the optimum level was 50% VO_{2max} in both sexes (Achten, Gleeson & Jeukendrup, 2001; Pillard et al., 2007).

Chapter 3. Methods

Background - The Full Plate Diet Study (FPDS)

In 2011-2012, researchers with the Human Performance Lab (HPL) at Southern Adventist University (SAU) identified an inverse relationship between health and fitness indices in sedentary, overweight or obese women. A vegetarian, high fiber diet was prescribed and the subjects were randomized into control (no exercise; FPD), continuous intensity (ConEX) or variable intensity (VarEX) exercise groups for an eight week exercise intervention. The VarEX group exercised at a higher intensity (67.7±5.8 %VO2max) and significantly improved their fitness (p <0.05, VO2max 20.8, 24.1, baseline, post-intervention respectively), while the ConEX group who exercised at a lower intensity (56.8±14.1 %VO2max) did not. Although the VarEX significantly lost more body weight (p <0.05, pounds 206.7, 203.0, baseline, post-intervention respectively) a significant body fat loss was only observed in the ConEX group (p <0.05, body fat % 35.2, 31.3, baseline, post-intervention respectively). Loss of body weight but not body fat % leads to the conclusion that there was an undesirable loss of FFM (Mayer et al., 2012).

Research Design

Research questions.

To follow up the unexpected inverse relationship identified in the FPDS, researcher's asked the following questions: 1. In overweight or obese women, is there a significant difference in metabolic health measures following high intensity or moderate intensity walking exercise interventions; 2. Do the metabolic health measures change significantly between moderate intensity intermittent and moderate intensity continuous walking exercise interventions; 3. Does a prescribed “whole foods whole” diet in a sedentary sample effect their RMR.

Randomized clinical trial.

Research design.

Answers to the research questions are best sought with a *quantitative, randomized clinical trial* (RCT), the hallmarks of which are randomization, manipulation and control. A quantitative study seeks empirical, plausible and consistent evidence for determining causality of the effects noted. In the evidence hierarchy, RCT’s are considered to be Level II evidence, with researchers adopting an active, as opposed to a passive observational, role in the experiment (Polit & Beck, 2008).

Randomization allocation and bias.

The process of randomization can be extremely complex and requires careful adherence to procedures that are designed to minimize challenges to the integrity of the study. Randomization should address potential within group confounders of the study sample and seek to eliminate as much bias as possible. The *allocation schedule* should be concealed from personnel enrolling study participants, preventing inappropriate and non-random treatment assignments and limiting *selection bias*. Ideally, the randomization would be performed by a third party not involved with the study (Moher et al., 2010).

Randomization - stratified permuted block.

Different schemes have been proposed to *stratify* the sample, through either individual assignments or in blocks of subjects; stratified permuted block randomization (sPBR) and *minimization* are two stratification techniques used. Stratified permuted block randomization groups ‘blocks’ of subjects based on similar characteristics and randomizes within that block. Selection bias is possible with sPBR if the block size and subjects’ assignments do not remain masked from the researchers (Matts & Lachin, 1988). Furthermore, researchers will need to use specific statistical tests to ensure that the analysis is not erroneously too conservative (Matts & Lachin, 1988).

Randomization – Minimization

Minimization is a more recent technique of *responsive adaptive randomization* and is gaining increased acceptance in the scientific community as a valid alternative for random assignment in clinical trials and is considered as “low risk of bias” (Moher et al., 2010; Higgins & Green, 2009). The minimization technique, described by Pocock and Simon (1975), assigns individual subject interventions based on a complex formula accounting for prior subjects’ assignments and predicting the next one that will balance treatment arms and strata. While dynamic block randomization was found to perform slightly better than minimization given smaller sample sizes, researchers noted that minimization may be more practical to implement (Xiao, Lavori, Wilson, & Ma, 2011).

Manipulation.

Manipulation of treatment arms is a required component of RCT’s and requires researchers to determine what treatment protocols will support answering the study questions. Treatment protocols define the specific manipulation of the study’s *independent variables* and development of those protocols involves researchers addressing a number of questions to ensure a technically valid and ethical RCT.

Treatment protocols will minimally stipulate what each intervention is, who and how they will be administered, and their duration, frequency and intensity. Ethically, researchers will need to identify how the experimental treatments differ from current standards of care, potential harms that subjects are exposed to from deviating from those standards, and fixed points for determining when to end or modify the study (Polit and Beck, 2009).

Control Condition.

The third item that identifies a RCT is the use of a control group for comparison when evaluating the treatment group's experimental data, providing baseline values for the *dependent variables*. While there are many strategies for defining a control group, ethical considerations will typically limit control group treatments in human studies to one or a combination of the following: Standard of care, alternative interventions, or the use of delayed treatments. Researchers need to be able to justify any harms or risks that potentially could occur from withholding treatments which they have theoretically determined would benefit the subjects (Polit & Beck, 2008).

Population

Study population.

As previously described, there is a significant *population* of overweight or obese women in the United States, most of who fail to meet current physical activity recommendations and are at considerable risk of declining metabolic health. Researchers sought to narrow the study population to middle adult obese and overweight women for a few reasons. First, this group should be able to provide a large enough *sample* of subjects with borderline metabolic dysfunctions, but absent overt disease. Secondly, exercise adherence and study attrition numbers should be reduced with this sample population, owing to their increased maturity and life experiences.

Experimental sampling and inclusion criteria.

The research design limited type of sampling techniques available to researchers. By defining the target population as noted, the study criteria produced a homogenous sample limited to subjects by age, gender and BMI. These three criteria were used in the marketing strategy which resulted in a combination of convenience and snowball nonprobability sampling. Further homogeneity among subjects was obtained through objective inclusion and exclusion criteria.

Selection bias from this sampling is considerable; conclusions can be drawn for the study sample, but generalization to the study population would be questionable. Self-selected subjects could possess greater exercise motivation and less exercise fear avoidance than the general population, leading to inflated health and fitness improvements.

Variables

Experimental dependent variables.

In a RCT, the *dependent variable* (DV) can be known by a few names, including response variable, outcome variable, measured variable and experimental variable. This is the measured condition that changes in response to the intervention. Researchers identified the variables of VO_{2max}, RMR, BF%, WT as the dependent variables of interest.

Experimental independent variables.

The *independent variable* is the condition that acts upon and is responsible for the changes in the DV. It is also known as the explanatory variable, the predictor variable, and the risk factor, among other names. Researchers are using the 'whole foods whole' diet, exercise intensity and type (continuous or intermittent) as independent variables.

Measurements

Assessment

Measurements are numerical values that have been assigned to specific items based on explicit rules. They can include objective items like values of blood pressure or weights, or subject items, such as feelings and motivations. Regardless of the type of item, all measurements have errors of measurement, of which the reliability and validity of the instruments impact greatly.

The reliability of an instrument refers to how consistently and accurately it is able to measure the item under observation. Reliability is determined by the equivalence, internal consistency and stability of the instrument, measured with Cohen's kappa, Cronbach's alpha, and the 'test-retest reliability' correlation coefficient, respectively (Polit & Beck, 2008).

The validity of a study can be inferred by examining how well the instrument measures what it appears to be (face validity) and if it measures a sample which is representative enough of the condition to surmise a measurement (content validity). Determining support for the validity of an instrument is a complex process and different techniques have been proposed (Polit & Beck, 2008).

Experimental measurements.

Physical Activity Readiness Questionnaire (PAR-Q).

The PAR-Q is a pre-participation health screening instrument which asks seven yes or no questions. The PAR-Q was developed by Chisholm et al. (1975) and had been found valid and reliable (Chisholm et al., 1978).

Anthropometric measurements.

The anthropometric measurements of height and weight are collected. A validated stadiometer is used to collect height measurements to the nearest ¼ inch and mechanical beam scale to obtain weights to the nearest four ounces (Health-O-Meter, model 402LB, McCook, IL, USA). Measurements are to be collected by trained laboratory assistants following the PhenX Toolkit measurements (Hamilton et al., 2011).

Metabolic measurements.

Resting metabolic rate, respiratory exchange ratio and maximal oxygen consumption are to be measured using an automated metabolic gas analysis system (Parvo Medics, Inc., TrueOne 2400, Sandy, UT, USA). This unit has been shown to be accurate and reliable (Crouter, Antczak, Hudak, DellaValle, & Haas, 2006; Macfarlane, & Wu, 2013). Body fat percentage is to be measured with the technique of hydrostatic body composition analysis using. Trained lab assistants will collect subject data using SAU HPL protocols.

Chapter 4. Results and Discussion

For this paper, the author was mentored as a research assistant by Dr. Harold Mayer, in the Human Performance Lab of SAU over a period of 12 months. During this time, the two met on average of once weekly and developed a follow-up study for the FPD. Topics discussed included evaluation of previous HPL research, poster presentation techniques, SAU Institutional Review Board (IRB) application and oversight processes, subject recruitment, budgeting and grant research and study management (Blair, 2012).

This mentorship provided the opportunity for the author to participate in metabolic testing with the same metabolic gas analyzer system used by NASA, the National Institutes of Health, and U. S. Olympic teams. The author was able to perform cleaning, calibration and operation of the system under direct supervision of the exercise physiologist. Submaximal and maximal treadmill exercise testing instruction according to ACSM guidelines was discussed at length and the author had the opportunity to observe and perform over 50 tests (Blair, 2012).

The author was tasked with evaluating previously analyzed data from the FPD study and generating graphs of significant results. These were eventually used in the creation of a poster for presentation by Dr. Mayer at the 59th Annual Meeting & 3rd World Congress on Exercise is Medicine® (Blair, 2012).

Following the May presentation, the author was tasked with researching for the follow up study of the FPD. There were meetings with representatives of SAU Corporate and Foundation Relations starting the grant request process. A Metabolic Study committee was formed and included members representing the fields of medicine, clinical nutrition, and nursing in addition to exercise physiology. This committee met weekly and developed a set of goals for the next study (Blair, 2012).

The author researched the SAU IRB application process and composed the application which was reviewed and approved. The author's research for this process required exploration of administrative requirements for a RCT. This included governmental regulations pertaining to human subject studies, HIPPA and subject privacy regulatory requirements, and the scientific community's CONSORT 2010 evaluation guidelines for peer reviewed publication of RCT (Moher et al., 2010).

Chapter 5. Evaluation

The opportunity to study as a research assistant under the mentorship of a professor active in research provided this author with an invaluable learning opportunity. While increasing personal knowledge of the current theories of exercise physiology, the most important educational value was being able to observe the process of developing a RCT through IRB approval and subject recruitment.

Significantly, the author came to develop an appreciation for the magnitude of work required to construct a RCT. Research on just one aspect, randomization, occupied a sizeable amount of time as certain schemes require researchers to incorporate specific statistical tests into their evaluation.

Physical activity is medicine for the illnesses of metabolic health. For too long, American society has misdirected their emphasis on weight loss or fitness improvement, while failing to stress metabolic health. Achieving this health in modern society is not plausible without modification of diet and PA lifestyle factors. Unfortunately, overweight or obese women face many barriers to increasing their physical activity.

As a result of the current research being conducted by the Human Performance Lab, there is new support for the concept that health and fitness goals diverge. On a practical level, this research provides a scientific basis for clinicians to encourage their patients to engage in physical activity with moderation to achieve the goal of lifelong metabolic health.

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Appendix A Metabolic Health Measures

Adiposity:

Hip circumference (cm)

Total body weight (kg)

Total body fat (%)

Total abdominal fat (TAT, cm2)

Total subcutaneous fat (TSAT, cm2)

Visceral fat (cm2)

Waist circumference (cm)

Waist / hip ratio

Lipoprotein Profile:

Apolipoprotein B (ApoB, mg / l)

Apolipoprotein A-I (ApoA-I, mg / l)

High density lipoprotein cholesterol (HDL-C, mg / dl)

HDL-C2 subfraction (mmol / l)

HDL-C3 subfraction (mmol / l)

Low density lipoprotein cholesterol (LDL-C, mg / dl)

Total cholesterol (mg / dl)

Triglycerides (TG, mg / dl)

Cardiorespiratory Fitness:

Diastolic BP (mmHg)

Systolic BP (mmHg)

Heart rate, resting (HR_{rest}, beats / min)

Heart rate, maximum (HR_{max}, beats / min)

VO2max, absolute (L / min)

VO2max, relative (ml · kg-1 · min-1)

Glycemic Regulation:

Glucose, fasting (FBG; mg / dl)

Insulin (uIU / ml)

Insulin resistance (HOMA)

Insulin sensitivity (QUICKI)

Systemic Inflammation:

Oxidized LDL-C (oxLDL, U / L)

C-reactive protein (CRP, mg / dl)

Tumor necrosis factor alpha (TNF-α, pg / ml)

Tumor necrosis factor receptor II (TNFRII, ng / ml)

Endocrine and Metabolic Fitness:

Thyroid-stimulating hormone (TSH, mcU / ml)

Triiodothyronine, total (T_3, ng / dl)

Thyroxine, free (FT_4)

Respiratory exchange ratio (RER)

Resting metabolic rate (RMR)