THE ROLE OF PHYSICAL ACTIVITY AND PHYSICAL FITNESS ON BIOMARKERS ASSOCIATED WITH DEPRESSION AND CARDIOVASCULAR DISEASE

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Dissertation Prepared for the Degree of

DOCTOR OF PHILOSOPHY

UNIVERSITY OF NORTH TEXAS

August 2016

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Barton, John Mitchell. *The Role of Physical Activity and Physical Fitness on Biomarkers Associated with Depression and Cardiovascular Disease*. Doctor of Philosophy (Educational Psychology - Psychological Aspects of Sport and Exercise), August 2016, 101 pp., 5 tables, references, 137 titles.

Two important health issues that can develop during young adulthood are related to mental health (e.g., depression) and physical health (e.g., cardiovascular disease). A common characteristic for both of these diseases is low-grade and chronic inflammation, but inflammation is negatively associated with physical activity (PA) and physical fitness. Thus, the purpose of this study was to investigate how PA and physical fitness were associated with biomarkers for depression and cardiovascular disease. Participants included 41 undergraduates who were considered to be “physical fit” ($n=21$, males = 15) or “physically unfit” ($n=20$, males = 17). They completed a battery of physical fitness assessments (e.g., 20m shuttle run, body fat percentage, handgrip strength, push-ups, blood pressure, and waist circumference), a self-report measure for depression and stress, and wore an accelerometer for one week. Afterwards, blood was drawn to estimate CVD risk using biomarkers for metabolic syndrome (i.e., triglycerides, glucose, and HDL) and inflammation (i.e., C-reactive protein [CRP], interleukin-6, interleukin-1b, and tumor necrosis factor alpha). The physically fit group had more moderate and vigorous PA, lower body fat percentage and handgrip strength scores, and performed better on the VO2max, curl-up, and plank tests compared to the physically unfit group. They also had a healthier profile for CVD (i.e., smaller waist circumference, lower triglycerides and glucose concentrations, higher HDL, and lower
CRP) and lower self-reported depression and stress scores compared to the physically unfit group.
ACKNOWLEDGEMENTS

I am indebted to many people for their help throughout the course of this project. First and foremost, I would like to thank my major professor, Dr. Scott Martin, for all of his assistance and guidance over the past several years and for his commitment to my success. He has always believed in me and been an invaluable resource during my graduate career. I will always be thankful for all that he has done. I owe my future successes to the work and time that he has invested in me.

I would also like to thank my other committee members for their time and suggestions with this project, which includes Dr. Whitney Moore, Dr. Jakob Vingren, and Dr. Wendy Middlemiss. In addition, I would like to thank the following people for their assistance during different stages of this project: Dr. Brian McFarlin, Dr. Allen Jackson, Dr. Beth Wright, Danielle Levitt, Jordan Travis, Dan Marshall, Veera Korjala, Chris Semler, Hui Ying Luk, Xiaoxia Zhang, Gene Farren, Paul Yeatts, Alan Chu, Andrea Henning, and John Curtis. Without their assistance, I would not have been able to overcome many of the barriers that I faced. Lastly, I would like to thank my wonderful wife for all of her support and patience with me from the beginning to the end of my graduate career. Her encouragement was a constant motivator even during the most challenging times, and I am very thankful for her love and support.
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Introduction

“Emerging adulthood” (i.e., 18-25 years old) has received increased attention in industrialized countries as an important transitional period for developing healthy behaviors and disease prevention (Arnett, 2000; Bureau of Labor Statistics, 2015; Nelson, Story, Larson, Neumark-Sztainer, & Lytle, 2008). A growing number of young adults experience mental health problems, such as depression (Eisenberg, Hunt, & Speer, 2013; Gallagher, 2014; Twenge et al., 2010). Young adults are also at greater risk for developing CVD because the prevalence of obesity in this age group has more than doubled over the past 30 years (Nelson et al., 2008). Furthermore, depression and CVD are projected to be the two largest causes of years lost due to ill-health, disability, or early death for all ages by 2020 (Reddy, 2010), and these health issues are related (i.e., depression can lead to CVD and vice versa; Blaine, 2008; Huffman et al., 2013; Van der Kooy et al., 2007). Thus, establishing effective and efficient methods to measure the severity of depression and CVD at an earlier age may help prevent or reduce the personal, social, and economic burden associated with these diseases (Buchan et al., 2011).

A common characteristic of both depression and CVD is the release of proinflammatory biomarkers, including acute phase proteins (C-reactive protein [CRP]) and cytokines (interleukin-6 [IL-6], interleukin-1β [IL-1β], and tumor necrosis factor alpha [TNF-α]; Blaine, 2008; Buchan, Thomas, & Baker, 2012; Buchan et al., 2011; Glynn, McFarlin, & Markofski, 2007; Huffman et al., 2013; Müller, Myint, & Schwarz, 2011; Van
der Kooy et al., 2007). While acute inflammation is a normal and beneficial response to infection or injury, excessive and chronic inflammation can lead to changes in the peripheral immune system and also to the development of other issues (e.g., atherosclerosis; Schiepers, Wichers, & Maes, 2005; Shrivastava, Singh, Raizada, & Singh, 2014). To illustrate how chronic exposure to inflammation (e.g., due to stress) can result in the development of depressive symptoms and CVD, Miller and Blackwell (2006) created an integrative conceptual framework. Their model illustrates how stressors can activate the immune system, which may lead to chronic inflammation. This process indicates that elevated concentrations of proinflammatory biomarkers from stress can elicit changes in the brain and promote the growth of plaque in arteries. The association between stress and proinflammatory biomarkers could provide a possible link between stress, immune function, and disease (e.g., depression and CVD). This is especially relevant for college students because they regularly face stressful situations (e.g., due to academic pressure, loneliness, and financial obligations; Eisenberg et al., 2013). Thus, even though CRP, IL-6, IL-1β, and TNF-α are not direct measures of depression or CVD, these biomarkers could provide information about whether increasing physical activity (PA) or improving fitness decreases chronic inflammation, resulting in improved health.

Depression

Previous attempts to identify a single biomarker to diagnose depression have been unsuccessful due to the heterogeneous nature of depression (Rao, 2013). Despite the difficulty in identifying a single biomarker, there is evidence that a panel of biomarkers could be used to identify the presence or absence of depression (Schmidt, Shelton, &
Duman, 2011), and proinflammatory biomarkers (e.g., CRP, IL-6, IL-1β, and TNF-α) are one of the most common types of biomarkers used to assess depression. Howren and colleagues (2009) recently conducted a meta-analysis of 136 studies that involved clinical or community adult populations to determine if there is a relation between depression and prominent biomarkers (e.g., CRP, IL-6, IL-1β). Using random-effects models, they combined effect sizes from all of the studies by using sample sizes to calculate weighted means. Their findings indicated that circulating concentrations of CRP, IL-6, and IL-1β were positively associated with depression. These findings were consistent across studies that used either clinical interviews (e.g., Miller, Stetler, Carney, Freedland, & Banks, 2002) or self-report measures (e.g., Taylor, Lehman, Kiefe, & Seeman, 2006) to measure depression.

Furthermore, a more recent meta-analysis by Haapakoski and Alenius (2015) indicated that depression was positively associated with CRP, IL-6, IL-1β, and TNF-α, but the strength of the relationships varied based on the method used to diagnose depression, the sample characteristics, and potential confounders. Previous research has also indicated that the acute administration of IL-6, IL-1β, and TNF-α can result in a group of symptoms known as “sickness behaviors”, such as anhedonia, fever, sleep changes, and decreased social interaction (Dantzer, Connor, Freund, Johnson, & Kelley, 2008). Similarities between these symptoms and depression has led to the proposal of the cytokine hypothesis for depression. Specifically, this hypothesis postulates that an increase in proinflammatory biomarkers can signal the brain to adopt these sickness behaviors. An increase in concentration of these biomarkers may play a
role in the pathology of depression because they positively correlate with the severity of depression (Schiepers et al., 2005).

CVD

Although the process is quite complex, there is evidence that immune pathways and inflammatory processes contribute to the development of CVD through atherosclerosis. Low-grade and chronic inflammation plays a role in CVD by leading to the deposit of plaque in the blood vessels (i.e., atherosclerosis), which can limit the supply of blood and oxygen to the heart (Shrivastava, Singh, Raizada, & Singh, 2014). This can result in an increase of proinflammatory biomarkers that eventually destabilize plaque and cause a cardiovascular event (Libby, 2012). To evaluate CVD risk, another risk factor besides inflammation that has received increased importance is metabolic syndrome (Galassi, Reynolds, & He, 2006). Based on the National Cholesterol Education Program’s Adult Treatment Panel-III (ATP III; National Cholesterol Education Program, 2002) metabolic syndrome can be diagnosed by having three or more of the following five indicators: high waist circumference, high blood pressure, high triglycerides, high fasting glucose, and low HDL. Galassi and colleagues (2006) conducted a meta-analysis with 21 studies to investigate the association between CVD and metabolic syndrome. They reported that having metabolic syndrome increased the risk of CVD by 61%, and metabolic syndrome was also associated with a higher relative risk for all-cause mortality (relative risk 1.35; 95% CI 1.17-1.56). One pathway that describes how metabolic syndrome affects CVD is through causing higher levels of inflammation in the body (Buchan et al., 2012). For example, higher concentrations of CRP have been identified in people with individual symptoms of metabolic syndrome.
(e.g., being overweight or hypertriglyceridemia) and may add clinically important
information to metabolic syndrome as an indicator for CVD (Ridker, Buring, Cook, &
Rifai, 2003). Although additional research is still needed, the positive associations
among inflammation, depression, and metabolic syndrome indicate that lower levels of
inflammation may be related to improvements in both diseases.

PA and Physical Fitness

Two possible options for decreasing chronic inflammation are regular PA (i.e.,
any bodily movement produced by skeletal muscles that results in energy expenditure)
and improved physical fitness (e.g., cardiorespiratory endurance; Caspersen, Powell, &
Christenson, 1985). Individuals with depression have elevated concentrations of CRP,
IL-6, IL-1β, and TNF-α (Eyre, Papps, & Baune, 2013; Howren et al., 2009). Regular PA
has been negatively associated with these biomarkers (Albert, Glynn, & Ridker, 2004;
Glynn et al., 2007; Hamer et al., 2012; McMurray & Andersen, 2010) and symptoms
related to CVD and metabolic syndrome (McMurray & Andersen, 2010; Sattelmair et al.,
2011; Thompson et al., 2003). For example, Hamer and colleagues (2012) collected
data on PA, CRP, and IL-6 for 4289 men and women over a 10-year period.
Participants who met the PA recommendations for 150 minutes of moderate and
vigorous activity at baseline had lower CRP and IL-6 concentrations than those who did
not achieve 150 minutes of activity per week. The results also indicated that maintaining
regular PA over the course of the study was associated with lower proinflammatory
biomarker concentrations. In addition, Sattelmair and colleagues (2011) conducted a
meta-analysis of 33 prospective cohort studies that investigated the dose-repose
relation between PA and CVD. Specifically, the authors investigated whether greater
amounts of PA were related to lower CHD risk. They reported that healthy individuals achieving at least 150 or 300 minutes of PA per week had a 14% and 20% lower risk for CVD compared to those who did not meet the guidelines, respectively.

While a greater number of studies focused on the role of PA, less information is available regarding the role of physical fitness, especially in populations that are very physically active. Physical fitness has historically reflected athletic performance (e.g., agility and speed), but since the 1970’s, more focus has been placed on aspects of health-related fitness (HRF), which includes cardiorespiratory endurance (or aerobic capacity), body composition, muscular strength and endurance, and flexibility (Jackson, 2006). The current literature has indicated that controlling for BMI reduces the effect size between CRP and depression by nearly two-thirds (Howren et al., 2009) and that cardiorespiratory fitness is negatively associated with CRP (e.g., Aronson et al., 2004; Lavie, Church, Milani, & Earnest, 2011). This indicates that it might be beneficial to consider the role of both PA and HRF with biomarkers for depression and CVD because improving HRF is an outcome of regular PA (Caspersen et al., 1985). Hence, more information is still needed in this area, especially during young adulthood when early signs of mental and physical health issues can occur. Thus, the purpose of this study was to investigate the association between PA and biomarkers related to depression and metabolic syndrome and if HRF moderates this association.

Methods

Participants

Forty-one undergraduates who were considered to be “physically fit” ($n = 21, M_{age} = 19.95 \pm 1.99, \text{Males} = 15$) or “physically unfit” ($n = 20, M_{age} = 20.35 \pm 1.84, \text{Males}$
They were recruited from seven sections of a health-related fitness course at a university in the southwest United States. While 59% of the participants were kinesiology majors, most students complete the course because they are interested in being more physically active, improving their physical fitness, and learning healthy behaviors. As a result, most students are engaged in regular PA during and outside of the class. Approximately 39% of the sample was white, 29% was Hispanic, 27% was African-American, 3% was Asian, and 3% were mixed, which was reflective of all sections of the class. Prior to data collection, study approval was received from the university Institutional Review Board, and all participants provided written informed consent after learning the requirements of the study.

To be classified as physically fit, the students had to meet both of the FitnessGram® requirements for aerobic capacity (i.e., functional or physiological capacity to perform large-muscle activity for a prolonged period of time; Plowman & Meredith, 2013) and body composition (i.e., components that make up body weight, including fat, muscle, and bone content; Institute of Medicine, 2012). Specifically, females needed an estimated VO$_{2\text{max}}$ ≥ 38.6 m$\text{l}$·kg$^{-1}$·min$^{-1}$ and body fat percentage between 16.5-31.3%, whereas the males needed an estimated VO$_{2\text{max}}$ ≥ 44.3 m$\text{l}$·kg$^{-1}$·min$^{-1}$ and body fat percentage between 7.0-22.2% to be classified as physically fit. By meeting these criterion-referenced standards, participants were considered to be in the Healthy Fitness Zone™ (HFZ) for each test. The HFZ represents the minimal level of fitness necessary to experience health benefits and to protect against diseases associated with sedentary living (Plowman et al., 2006). If participants did not meet both of these standards, then they were classified as physically unfit. Also, if they met the
HFZ for only one of the tests, then they did not qualify for this study. While no one was excluded based on race or ethnicity, all participants were between the ages of 18-25 years old because there has been mixed evidence on inflammation increasing as individuals get older (Howren et al., 2009). In addition, all females were eumenorrheic and not pregnant or trying to become pregnant.

**Measures**

*Demographics.* The participants self-reported their gender, age, and ethnicity. In addition, participants completed a medical history form that included information about whether they or family members (e.g., parents) had ever been diagnosed with a physical (e.g., heart disease) or mental (e.g., depression) illness and whether they were currently using tobacco, marijuana, or medications. Females also reported their birth control use and current menstrual cycle because these factor can influence levels of inflammation (Wander, Brindle, & O’Connor, 2008).

*Physical activity.* Actical accelerometers (Philips Respironics Inc., Bend, OR) were used in this study (John & Freedson, 2012). Participants wore the accelerometer on their non-dominant wrist for eight consecutive days (Heil, Brage, & Rothney, 2012), and previous research indicates that Actical accelerometers are valid in measuring time spent in light, moderate, and vigorous PA in adults (Heil, 2006). The first seven days were used to measure their PA levels during a typical seven-day period (e.g., no holidays; Heil et al., 2012). Participants were told on the eighth day to not exercise for 24 hours before the blood sample so that PA would not affect the inflammatory biomarkers. This also prevented the groups from engaging in significantly different amounts of PA prior to the blood draw. Accelerometer data was collected at 60-second
epochs, and all participants provided at least six days with 10 hours of daily recordings, including at least one weekend day, which is in accordance with previous research with adults (Downs, van Hoomissen, Lafrenz, & Julka, 2014; Hagströmer, Troiano, Sjöström, & Berrigan, 2010; Trost, Mciver, & Pate, 2005). Non-wear time was not included in the analysis and was defined as zero activity counts for at least 60 consecutive minutes (Downs et al., 2014). Participants were also given a daily log to record when they were asleep and when they took off the accelerometer each day so that this data would not be included. The amount of light (100–2,019 counts/minute), moderate (2,200–5,998 counts/minute), and vigorous (> 5,999 counts/minute) PA was determined using the National Health and Nutrition Examination Survey (NHANES) cut points (Troiano et al., 2008). These standards have been used previously in a study with a similar population (Downs et al., 2014). The activity counts were used to determine the average percentage of time spent in light, moderate, and vigorous activity each day.

*Body composition.* Body fat percentage was measured using the Omron HBF-360C Fat Loss Monitor. It is a hand-held device that measures body fat using bioelectrical impedance (Ayvaz & Çimen, 2011). Previous research with this device has found evidence of concurrent validity with dual-energy, x-ray absorptiometry, or DEXA, for both men and women (*r* = .78, .74) and good repeatability (CV = 0.6%; Jensky-Squires et al., 2008). Bioelectrical impedance was chosen because it is one of the methods used to determine body composition according to the FitnessGram standards (Plowman & Meredith, 2013).

*Progressive Aerobic Cardiovascular Endurance Run (PACER).* The PACER test is a 20-meter shuttle run that has been widely used to measure aerobic capacity and
has sufficient reliability and validity (Plowman & Meredith, 2013). It is a progressive, multistage maximal exercise test. Previous research has found test-retest coefficients greater than .68 and validity coefficients ranging from .83 to .93 when comparing the PACER to direct measures of VO$_{2\text{max}}$ (Plowman & Meredith, 2013). The goal of the PACER is to run back and forth across a 20-meter distance at a specified pace as many times as possible. The pace gets progressively faster after each minute, and the number of laps that participants achieve were used to estimate VO$_{2\text{max}}$ (Plowman & Meredith, 2013).

**Metabolic syndrome.** Metabolic syndrome was used to assess CVD risk because previous research has indicated that metabolic syndrome is an important risk factor for CVD (Galassi et al., 2006). Metabolic syndrome was determined using the guidelines set by the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III; Grundy et al., 2005; National Cholesterol Education Program, 2002). To be diagnosed with metabolic syndrome, at least three or more of the following must be present: (a) waist circumference > 102 cm in men and > 88 cm in women, (b) triglyceride level $\geq$ 150 mg/dL or currently being treated with drugs, (c) HDL < 40 mg/dL in males and < 50 mg/dL in women or currently being treated with drugs, (d) blood pressure $\geq$130/85 mmHg or currently being treated with drugs, and (e) fasting glucose $\geq$ 100 mg/dL or currently being treated with drugs. Serum samples were analyzed for triglycerides, HDL, and fasting glucose using enzymatic assays (Pointe Scientific, Canton, MI) and an automated chemistry analyzer (ChemWell-T, Awareness Technology, Inc. Palm City, FL).
**Proinflammatory biomarkers.** Four proinflammatory biomarkers related to depression and CVD were collected through venous blood draws. These included CRP and the following cytokines: IL-6, IL-1β, and TNF-α. All samples were analyzed in duplicates. CRP was analyzed using a commercially available high-sensitivity ELISA (DRG International, Inc.). Serum samples were analyzed using a microplane spectrophotometer (PowerWave 340, Biotek, Inc. Winooski, VT), and the concentration of CRP was calculated using Gen5 software version 2.08 (Biotek, Inc. Winooski, VT). For the cytokines, supernatant was thawed and diluted (1:5) with assay buffer (MILLIPLEX MAP Assay Buffer, EMD Millipore, Billerica, MA). Using a commercially available human high-sensitivity cytokine assay (HSCYTMAG-60SK, EMD Millipore, Billerica, MA), a Luminex-based system (Magpix, Luminex, Austin, TX) was used to measure IL-6, IL-1β, and TNF-α. Concentrations of the cytokines were calculated using MILLIPLEX® Analyst software (EMD Millipore, Billerica, MA). The intra-assay coefficients of variation ranged from 13.1% to 18.7% for each analyte. Due to the small concentrations of each analyte, small differences across some of the duplicate samples inflated the coefficient of variation.

*Depression, Anxiety, and Stress Scale (DASS-21).* The DASS-21 (Antony, Bieling, Cox, Enns, & Swinson, 1998) is a short form of the DASS (Lovibond & Lovibond, 1995) that measures negative affect over the past week. One of the benefits of the DASS-21 is that it takes less time to complete and has a stronger factor structure than the original scale (Crawford, Cayley, Lovibond, Wilson, & Hartley, 2011; Henry & Crawford, 2005). For the purposes of this study, only the 14 items from the depression and stress subscales were used. The DASS-21 uses a 4-point Likert-type response
scale from 0 (*Did not apply to me at all*) and 3 (*Applied to me very much, or most of the time*). Crawford and colleagues (2011) found Cronbach’s alpha with an adult population to be .90, 95% CI [.89, .91], for the depression subscale and .89, 95% CI [0.88, 0.90], for stress subscale. In the current study, Cronbach’s alpha was found to be .81 and .79 for the depression and stress subscales, respectively.

**Procedures**

Students in each section of the health-related fitness course completed a battery of fitness tests as a requirement for the course (e.g., body fat percentage and 20-meter shuttle run) at the beginning of the semester. Beforehand, students were recruited through a face-to-face class announcement for the opportunity to participate based on their fitness testing performance. Students were told that if they qualified and chose to participate that they would receive a $50 gift card. However, the specific requirement of meeting both or neither of the VO$_{2\text{max}}$ and body composition standards was not shared to prevent students from purposefully changing their level of effort during the fitness testing. One-hundred and ninety of the 251 students in the course (76%) signed up to participate. After the fitness testing, they completed the stress and depression items from the DASS-21 online, but only 68 of the participants who volunteered for the study met both or neither of the VO$_{2\text{max}}$ and body composition standards. These participants were told that they had passed the initial qualification of the study, and they arranged a time to complete the medical history form. Eight participants did not respond to the text message, and 14 could not participate after completing the medical history form due to injury, scheduling conflicts, smoking behaviors, anti-inflammatory medication, or birth control that drastically altered their menstrual cycle. The remaining 46 participants were
included in the study, but five participants dropped out during the course of the study due to injury or sickness, which resulted in a final sample of 41 participants.

The participants arrived between 7 and 14 days after the fitness testing to receive the accelerometer. When they arrived, the participant’s blood pressure was recorded based on guidelines set by the American Heart Association (Pickering et al., 2005), and their waist circumference was measured to nearest tenth of a centimeter. After these measurements were taken, the accelerometer was placed on their non-dominant wrist. The students were told to maintain their normal schedule for the next seven days. They also received a daily log and were instructed to record when they slept and took off the accelerometer each day. In preparation for the blood draw and to limit the effect of external factors on the blood sample, the participants were asked to abstain from using tobacco, marijuana, or anti-inflammatory medication while they wore the accelerometer.

After wearing the accelerometers for eight days, participants arrived between 8:00 am and 9:20 am after an overnight fast to return the accelerometer and provide the blood sample. All blood samples for females were collected 7 to 14 days after their last menses to control for menstrual cycle (Wander et al., 2008). Prior to sampling, participants sat quietly for at least 10 minutes to control for plasma volume shifts. Then, approximately 18 mL of blood was drawn from an antecubital vein by trained technicians using sterile technique. All samples were allowed to clot for 20 minutes and were then centrifuged for 20 minutes at 1500g at 4° Celsius. The serum samples were aliquoted and stored at -80° Celsius until they were later thawed for analysis.

Statistical Analysis
Data was managed and analyzed using SPSS version 22. First, the following statistical information was examined: skewness on all variables; means, standard deviations, and correlations for PA, HRF, biomarker concentrations, and the depression and stress scores; and internal consistency of the DASS-21 subscales. The level of significance for all tests was set at .05.

Second, a series of one-way ANOVAs were conducted with the physically fit and physically unfit groups as the independent variable and light, moderate, and vigorous PA as the outcome variables. A priori power analysis using G*Power3 indicated that an effect size of .45 for Cohen’s $f$ was needed to achieve a statistical power of .80 (Faul, Erdfelder, Lang, & Buchner, 2007). It was hypothesized that the physically fit group would engage in more moderate and vigorous PA than the physically unfit group. Two additional one-way ANOVAs were conducted with the depression and stress subscales of the DASS-21. Third, three canonical correlations were conducted with the three PA variables as the predictors. Three separate composites of the proinflammatory biomarkers, metabolic syndrome biomarkers, and DASS-21 subscales were used as the outcome variables. Due to its anti-inflammatory effects, the PA variables were hypothesized to be negatively related to CRP, IL-6, IL-1β, and TNF-α. PA was also expected to be negatively related to waist circumference, blood pressure, triglycerides, fasting glucose, but positively related to HDL. Higher levels of PA were also expected to be negatively associated with self-reported levels of depression and stress.

Fourth, a hierarchical multiple regression for each biomarker was conducted to determine if fitness level moderated the relationship between PA and the biomarkers. A priori power analysis using G*Power3 indicated that a Cohen’s $f^2$ effect size of .30 or
greater was needed to achieve a power of .80. The moderate and vigorous PA variables were combined into a single variable (i.e., MVPA) that represented the average percentage of time spent in MVPA. To create the interaction variable, MVPA was first mean-centered, and a dummy code variable was created with the physically fit group as the reference group. The mean-centered MVPA and dummy code variable were then multiplied together. MVPA and the grouping variables were entered at Step 1, and the interaction variable was entered at Step 2.

It was hypothesized that physical fitness would moderate the relationship between MVPA and each biomarker. Specifically, higher levels of MVPA would have less of an effect on each biomarker in the physically fit group compared to the physical unfit group. Lastly, two final hierarchical multiple regressions were conducted to determine if fitness level moderated the relationship between MVPA and self-reported depression and stress. The MVPA and dummy code variables were entered at Step 1 to determine if they were negatively associated with self-report scores for depression and stress, while the interaction variable was entered at Step 2 to test for moderation.

Results

Descriptive Statistics

After examining the skewness for all variables, a Box-Cox transformation was performed on variables with a skewness greater than .80 or less than -.80 (Osborne, 2010). This included the following variables: push-up, plank, waist measurement, triglycerides, glucose, HDL, CRP, IL-6, IL-1β, TNF-α, depression, and stress. As a result, the transformed skewness ranged from -.07 to .12 after using a λ between -2.0 and 1.8. Descriptive statistics included mean values (see Table 1) and correlations (see
Table 2) for physically fit and physically unfit participants. Based on recommendations from previous research (Osborne, 2010), the raw data prior to the transformations is provided in Table 1 to improve the interpretability of the results, but the correlations were derived from the transformed data. The variables included PA, body composition, VO$_{2\text{max}}$, metabolic syndrome (i.e., waist circumference, triglycerides, HDL, blood pressure, and fasting glucose), CRP, cytokines (i.e., IL-6, IL-1β, and TNF-α), and the depression and stress subscales from the DASS-21. The Pearson $r$ correlations indicated that the strength of the correlations varied based on the fitness level of the participants. For example, none of the proinflammatory biomarkers were significantly correlated to the mean scores for the depression or stress subscales of the DASS-21 in the physically fit group, and only TNF-α was significantly correlated to one of the other proinflammatory biomarkers (i.e., IL-6; $r = .67$, $p < .01$). In the physically unfit group, IL-6 was significantly correlated ($p < .05$) with CRP ($r = .50$), TNF-α ($r = .68$), depression ($r = .59$), and stress ($r = .48$). TNF-α was also positively correlated to depression ($r = .45$).

Participants’ responses on the medical history of their immediate family members (i.e., parents, siblings, or grandparents) indicated that 20% of the participants had a family member with heart disease, 54% with diabetes, 17% with stroke, 46% with high blood pressure, and 20% with high cholesterol or triglycerides. In addition, 10%, 7%, and 10% of participants reported that an immediate family member had been diagnosed with anxiety, depression, or other mental illness, respectively. In regards to all participants, 7% self-reported that they had been diagnosed with high blood pressure, 2% with high cholesterol or triglycerides, 5% with low HDL, 7% with anxiety, and 5% with depression. However, 80% of the physically unfit participants exhibited at least two
symptoms for metabolic syndrome, and 44% of those participants met the requirement for at least three symptoms. Specifically, 33% of the physically unfit participants had high waist circumference, 33% high systolic or diastolic blood pressure, 0% high triglycerides, 45% low HDL, and 3% high glucose. Furthermore, the physically fit group had lower mean values for inflammatory biomarkers than the physically unfit group. Specifically, the percent difference between the physically fit and unfit participants for the mean concentrations of CRP, IL-6, IL-1β, and TNF-α was approximately 89%, 28%, 6%, and 70%, respectively.

Primary Statistics

First, to determine if the physically fit and physically unfit groups differed in their levels of light, moderate, and vigorous PA, three one-way ANOVAs were used. While the fitness groups did not differ in their amount of light PA ($p = .65$), the difference for both moderate, $F(1, 39) = 3.97, p = .05$, and vigorous $F(1, 39) = 3.95, p = .05$, PA was statistically significant with an overall $\eta^2$ effect size of .10 and .09, respectively. The average percentage of time that the physically fit group spent in moderate (Cohen’s $d = .62$) and vigorous PA (Cohen’s $d = .62$) was more than the physically unfit group. Despite these differences in moderate and vigorous PA (MVPA), both groups largely exceeded the 2008 Physical Activity Guidelines (U.S. Department of Health and Human Services, 2008). Specifically, the physically fit group engaged in $181.12 \pm 93.60$ and $11.83 \pm 13.72$ minutes of moderate and vigorous activity on average per day, whereas the physically unfit group had an average of $134.75 \pm 45.73$ and $7.99 \pm 11.14$ minutes of moderate and vigorous activity, respectively. This highlights that both groups engaged in high levels of regular PA despite differences in their fitness level. Second, three
canonical correlations were used to investigate the multivariate relationship between a composite of light, moderate, and vigorous PA with each of the three following sets of variables: metabolic syndrome variables, proinflammatory biomarkers, and the DASS-21 subscales for depression and stress. The PA variables from the physically fit and physically unfit groups were combined because both met the PA guidelines. None of the canonical correlations associating PA with the metabolic syndrome variables, Wilks’ $\lambda = .48$, $F(18, 90.99) = 1.50, p = .11$; proinflammatory biomarkers, Wilks’ $\lambda = .79$, $F(12, 90.25) = .68, p = .76$; or depression and stress subscales, Wilks’ $\lambda = .95$, $F(6, 72) = .12, p = .94$, were statistically significant.

Lastly, a hierarchical multiple regression for each of the metabolic syndrome and proinflammatory biomarkers was conducted to determine if fitness level moderated the relationship between MVPA and each biomarker. While the previous analyses used the transformed data, the raw data was used to improve the interpretability of the regression coefficients because the transformed dependent variables did not change the statistical significance of the results (Osborne, 2010; see Table 3). The results indicated that the full models for waist circumference, diastolic blood pressure, triglycerides, HDL, and glucose were statistically significant ($p < .05$) with $R^2$ values ranging from .20 to .64. The fitness group variable was a statistically significant predictor ($p < .05$) for all of these models. Specifically, the physically unfit group had higher scores for waist circumference ($B = 39.73$), triglycerides ($B = 44.73$), glucose ($B = 20.85$), and lower scores for HDL ($B = -42.92$). These findings were also supported after examining the structure coefficients for fitness group ($r_s$; i.e., the correlation between each independent variable and the predicted $\hat{Y}$ scores for each biomarker), which ranged from .74 to .98.
While MVPA was not a significant predictor for any of the models, the structure coefficients for MVPA in the waist circumference ($r_s = -0.36$) and triglycerides ($r_s = -0.61$) models were lower than the unstandardized regression coefficients. Because MVPA was significantly correlated to fitness group ($r = -0.35$) and the interaction term (i.e., $r = 0.61$), these other variables received more credit than MVPA in the regression equation because they had a stronger correlation with $\bar{Y}$ than MVPA. The only statistically significant interaction effect was found for triglycerides $\Delta R^2 = 0.13$, $F(1, 37) = 8.29$, $p < 0.001$, which indicated that the interaction variable accounted for an additional 13% of variability in triglycerides with an effect size of $f^2 = 0.22$. Specifically, there was a statistically significant negative relationship between PA and triglycerides for the physically unfit participants, whereas the physically fit participants had a consistent level of triglycerides regardless of their level of PA. None of the remaining regression analyses (i.e., systolic blood pressure, CRP, IL-6, IL-1β, TNF-α, and self-reported depression and stress) were statistically significant ($p > 0.05$) with $R^2$ values ranging from 0.03 to 0.11.

Discussion

The main aim of the present study was to investigate the role of PA and HRF with biomarkers related to depression and metabolic syndrome in a sample of physically fit and unfit young adults who engaged in regular PA. Regarding the proinflammatory biomarkers for the physically unfit group, IL-6 was significantly correlated to CRP, TNF-α, depression, and stress. TNF-α was also significantly correlated to depression. None of these biomarkers were statistically significant in the physically fit group except for the correlation between IL-6 and TNF-α. While the physically fit students participated in
more moderate and vigorous activity than the physically unfit students, MVPA was not a significant predictor of biomarkers for metabolic syndrome or inflammation. On the other hand, HRF was a significant predictor for waist circumference, triglycerides, glucose, and HDL. Specifically, participants who were physically unfit had higher waist circumference, triglycerides, glucose, and lower concentrations of HDL than the physically fit students. In addition, PA was a stronger predictor of triglycerides for the physically unfit participants compared to those who were physically fit.

These results provide initial evidence that it might be important to consider HRF when measuring proinflammatory biomarkers in young adults, even when they exceed the PA guidelines. The participants in the current study likely engaged in high levels of PA for several reasons. First, the structure of the class provided participants with the opportunity to exercise twice a week. Second, many of the students were also kinesiology students so they were likely active in other PA classes or during their leisure time. Third, the nature of the study may have led to selectivity bias where those who volunteered were more likely to be physically active or interested in improving their health behaviors. As a result, wearing a device that monitors PA may have led to a reactivity response that increased their PA behaviors (Clemes & Deans, 2012; Clemes & Parker, 2009).

Obesity has been described as a chronic, low-grade metabolic inflammatory state in response to excess nutrients in metabolic cells (Gregor & Hotamisligil, 2011). This inflammatory state, which is indicated by elevated concentrations of proinflammatory biomarkers (e.g., CRP, IL-6, and TNF-α; Gleeson et al., 2011), has also been linked to chronic diseases, such as depression and CVD. For example,
Gregor and Hotamisligil (2011) discussed how eating can result in an inflammatory response in the cells of lean, healthy individuals that is quickly resolved. However, in obese individuals, the inflammatory response can be more intense and frequent until it eventually leads to the recruitment of other metabolic cells that exacerbate this inflammation (e.g., macrophages and T cells). Thus, if inflammation is affected by how cells react to excess nutrients, then anti-inflammatory treatments might be beneficial to treat depression and CVD (Gregor & Hotamisligil, 2011). This has implications for both PA and HRF as possible treatments due to their anti-inflammatory effects.

Previous research has generally indicated that there is a negative relationship between PA and inflammation (e.g., CRP; Albert et al., 2004), but not all support this association (e.g., Lund, Hurst, Tyrrell, & Thompson, 2011). One of the limitations with many of these studies is the use of self-report measures for PA (Loprinzi et al., 2013). In fact, a review by Hamer (2007) of 20 studies that investigated the relationship between fitness and fatness with inflammation all used a self-report measure for PA. Reliability and validity issues are important to consider when using self-report PA measures, such as overestimating PA, social desirability bias and recall error, and inability to measure absolute levels of PA (Prince et al., 2008; Shephard, 2003). Celis-Morales and colleagues (2012) suggested that these issues can make it difficult to accurately measure PA’s association with metabolic and CVD risk factors or may underestimate the strength of those relationships. Thus, there is a need for additional research investigating the relationship between objectively measured PA (e.g., accelerometers) and proinflammatory biomarkers.
To address this concern, Loprinzi and colleagues (2013) conducted a study to investigate the dose-response relationship between objectively-measured PA and CRP. They used accelerometer and biomarker data from a nationally representative sample of 4,555 children and middle-aged adults in the 2003-2004 National Health and Nutrition Examination Survey. An inverse relationship between PA and CRP was reported for middle-aged adults but not children. While age-related differences have been found with CRP, Glynn and colleagues (2007) suggested that higher levels of overall PA might account for these changes because younger populations generally engage in more PA than older populations. This was corroborated by Loprinizi et al.’s (2013) study, which revealed that the mean duration of MVPA for children was eight times longer than for middle-aged adults. These findings were supported by the current study, which also used accelerometers to measure MVPA. In the current study, physically fit students participated in significantly more moderate and vigorous PA, but the average time spent in moderate and vigorous activity for both groups was over 140 minutes each day. Thus, the high level of PA for both groups might explain why a relationship between PA and the proinflammatory biomarkers was not found. This also indicates that overall PA might explain the age-related differences in CRP because the young adults in the current study were closer in age with the children in Loprinzi et al.’s (2013; $M_{age} = 12.16 \pm 0.21$) study than with the middle-aged adults ($M_{age} = 48.29 \pm 0.47$).

Despite PA not being a significant predictor in the current study, differences were found between physically fit and physically unfit participants on CRP, IL-6 and TNF-α. These differences are supported by previous research because TNF-α is positively associated with IL-6 production, and IL-6 stimulates CRP production in the liver (Pepys
In addition, Casey (2013) conducted a study with 96 participants who were enrolled in phase-II cardiac rehabilitation to investigate how physical fitness is related to depression and inflammation. The author found evidence that physical fitness moderated the relationship between depression and IL-6. Specifically, a positive relationship between depression and IL-6 was found for those with lower levels of physical fitness. Thus, improving HRF may be another beneficial alternative for those who do not wish to use medication or have not responded strongly to drug therapy (Casey, 2013).

The primary strength of the current study was the use of objective measures for physical and mental health, including accelerometers, fitness assessments, and biomarkers. This reduced many of the common limitations associated with self-report measures (e.g., social desirability bias and incorrect recall). Second, several confounding variables were controlled in the study design to limit their effect on the results, such as age, smoking and alcohol behaviors, exercising within 24 hours of the blood sample, menstrual cycle, medications, sickness, and injury. This decreased the likelihood that these variables affected the results of the study. Third, this study used separate criterion-referenced standards for males and females on both body composition and aerobic capacity to help ensure that the groups were different from each other. This improved the statistical power of the study by creating greater differences between the groups.

While there were several strengths associated with this study, there were some limitations to consider. First, the sample size of the current study was limited due to the cost of analyzing the biomarkers. To address this issue and to increase statistical
power, only students who met both or neither of the HRF standards for aerobic capacity and body composition were eligible to participate, and accelerometers were used to get a more objective and accurate measure of PA compared to self-report questionnaires. Because the physically unfit group had lower levels of PA, more symptoms of metabolic syndrome, higher mean values for proinflammatory biomarkers, and higher scores on depression and stress compared to the physically fit group; future research with larger samples may result in additional statistically significant findings. Second, the self-report measure for depression and stress may be susceptible to self-desirability bias. While the current sample included young adults with metabolic syndrome, it was not drawn from a population who had clinical mental health issues. As previously mentioned, participants in this study were also recruited from a health-related fitness class. As a result, even many of the physically unfit students were regularly physically active during the testing period. Thus, future researchers should recruit individuals reporting a greater range of mental health symptoms and engaging in varying levels of PA than those in the current study.

Third, it is possible that some participants were not fully motivated to perform well during the fitness tests. To address this issue, the lead investigator administered the fitness testing to ensure that the testing environment was consistent for all the classes. Consistent feedback and encouragement was presented to the participants as they completed the tests to help them to stay motivated. Future research is needed to determine whether participant motivation during fitness testing impacts the relationship between HRF and the biomarkers. Lastly, the inflammation and metabolic syndrome
biomarkers were not direct measures of depression and CVD, but they are related to preventative risk factors for these diseases.

Conclusion

In a physically active sample of physically fit and unfit young adults, PA had less of an effect than HRF on variables associated with metabolic syndrome and depression. Specifically, for physically unfit participants, IL-6 was significantly correlated to CRP, TNF-α, depression, and stress. TNF-α was also correlated to depression. The physically unfit group also had significantly higher scores for waist circumference, triglycerides, glucose, and lower scores for HDL. Even though the physically fit students engaged in significantly more moderate and vigorous PA, the lack of an association between PA and the biomarkers was likely due to the high levels of MVPA in both groups. Future research should continue to collect more objective data (e.g., accelerometers, HRF, and biomarkers) and to recruit samples with more clinical symptoms of depression and stress.
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THE ROLE OF HEALTH-RELATED FITNESS ON BIOMARKERS ASSOCIATED WITH DEPRESSION AND CARDIOVASCULAR DISEASE

Introduction

Depression is recognized as one of the most prevalent types of mood disorders today (Blumenthal et al., 2005). Current estimates indicate that 17% of the United States population (between 5-12% of men and 10-20% of women) will experience a major depressive episode at least once in their lifetime (Blumenthal et al., 2005; Kessler et al., 2005). Furthermore, depression is projected to trail only cardiovascular disease (CVD) in years lost due to ill-health, disability, or early death for all ages by 2020 (Reddy, 2010). This is important for young adults because the majority of mental disorders first occur before or during the typical college age (Kessler et al., 2005). The prevalence of obesity in young adults has also more than doubled over the past 30 years, which increases their risk for developing CVD (Nelson et al., 2008). Previous research has also indicated that depression and CVD are interrelated (i.e., depression can lead to CVD and vice versa; Blaine, 2008; Huffman et al., 2013; Van der Kooy et al., 2007). Thus, effective and efficient methods are needed to measure the severity of these diseases and to treat accordingly.

Depression

Clinicians usually measure depression from multiple perspectives (e.g., self-report questionnaires and interviews), but there is an ongoing debate about the objectivity of these approaches (Lopresti, Maker, Hood, & Drummond, 2014). Due to the heterogeneous nature of depression, it can be difficult to diagnose in real-world settings, which can delay possible treatment and lead to worse outcomes (Carvalho et al., 2014;
One option suggested to aid in the diagnosis of depression is the use of biomarkers (i.e., indicators of normal, pathogenic, or pharmacological processes that can be measured objectively; Lopresti et al., 2014). Similar to how genetics tests are conducted to identify possible illnesses later in life, biomarkers could potentially help clinicians understand the biological causes of depression. Using biomarkers could provide additional information rather than solely using subjective assessments. Biomarkers for other diseases have been used to successfully diagnose illness, predict treatment, measure treatment progress, and predict future onset (Lopresti et al., 2014).

Unfortunately, previous research has been unable to identify a single biomarker to diagnose depression due to its heterogeneous nature (Rao, 2013). Instead, a panel of biomarkers might be helpful to identify the presence or absence of depression (Schmidt et al., 2011). For example, there is evidence that proinflammatory biomarkers, including C-reactive protein (CRP), interleukin-6 (IL-6), interleukin-1β (IL-1β), and tumor necrosis factor alpha (TNF-α), are positively associated with depression symptoms (Eyre et al., 2013; Lopresti et al., 2014; Müller et al., 2011; Rao, 2013). Furthermore, prolonged exposure to stress can lead to the production of proinflammatory biomarkers that increase a person’s risk for developing depression (Eyre & Baune, 2012; Stepanichev, Dygalo, Grigoryan, Shishkina, & Gulyaeva, 2014). This is especially relevant for college students, who regularly face many different stressors, such as academic pressure, loneliness, and financial obligations (Eisenberg et al., 2013). To investigate the relationship between depression and proinflammatory biomarkers (i.e., CRP, IL-6, and IL-1β), Howren and colleagues (2009) conducted a meta-analysis with 136 studies. They included studies with clinical and community adult populations that
measured proinflammatory biomarkers in circulating peripheral blood. The effect sizes across all of the studies were combined using sample sizes to calculate weighted means. The results indicated that depression was positively associated with proinflammatory biomarkers. In addition, the authors reported that these positive relations were present when using clinical interviews (e.g., Miller, Stetler, Carney, Freedland, & Banks, 2002) or self-report questionnaires (e.g., Taylor, Lehman, Kiefe, & Seeman, 2006) to measure depression.

CVD

In regards to the role of proinflammatory biomarkers with CVD, Buchan and colleagues (Buchan et al., 2011) highlighted the need to identify risk factors associated with CVD as early as possible. This is because approximately 50% of CVD incidents occur in individuals who have few or no signs of the traditional risk factors (Shrivastava et al., 2014), and there is growing evidence that risk factors can appear in early childhood and persist through the lifespan (Buchan et al., 2011; Saland, 2007). One important risk factor for CVD is metabolic syndrome, which is diagnosed when exhibiting three or more of the following five indicators: high waist circumference, high triglycerides, high blood pressure, high fasting glucose, and low HDL (National Cholesterol Education Program, 2002). Due to the relation between metabolic syndrome and CVD, these indicators can be used to estimate a person’s CVD profile because metabolic syndrome can increase the risk of CVD by 61% (Galassi et al., 2006). In addition, higher concentrations of CRP are associated with individual symptoms of metabolic syndrome (e.g., overweight or hypertriglyceridemia; Ridker et al., 2003). This opens the possibility that proinflammatory biomarkers (e.g., CRP, IL-6,
IL-1β, and TNF-α) may add clinically important information to metabolic syndrome and improve CVD risk assessment. While inflammation and metabolic syndrome are not a direct measure for depression or CVD, low-grade and chronic inflammation is related to preventative risk factors associated with both of these diseases (Buchan, Thomas, et al., 2012; Müller et al., 2011). Thus, measuring proinflammatory biomarkers could provide information about the role of physical fitness on decreasing the concentration of these biomarkers.

Physical Fitness

A number of studies have investigated the effect of physical activity (PA) and exercise on inflammation (Glynn et al., 2007), but more information is still needed regarding the role of physical fitness (Buchan et al., 2012). While physical fitness originally referred to aspects of athletic performance (e.g., power and reactivity), health-related fitness (HRF; e.g., cardiorespiratory endurance [or aerobic capacity], body composition, muscular strength and endurance, and flexibility) is a more common measure of physical fitness (Jackson, 2006). For example, Becofsky and colleagues (2015) found that low cardiorespiratory endurance was a stronger indicator of the onset of depression than any measure of fatness in middle-aged adults. However, they used a self-report measure for depression. Hence, additional information is still needed regarding the relationship between HRF and proinflammatory biomarkers for depression at different life stages, such as emerging adulthood. Compared to depression, the relationship between HRF and CVD has been more widely studied. There is consistent evidence that low levels of fitness (e.g., poor cardiorespiratory endurance and high body fat percentage) corresponds with a greater risk of CVD (Carnethon et al., 2003).
However, few researchers have investigated the possible relationship between HRF and proinflammatory biomarkers (e.g., Andersen et al., 2010; Nemet et al., 2003). In addition, previous research has largely focused on either cardiorespiratory fitness or body composition (e.g., Janssen & Cramp, 2007; Christou, Gentile, DeSouza, Seals, & Gates, 2005). No studies were found that investigated the role of other aspects of HRF. Thus, the purpose of this study was to investigate the association between different components of HRF and proinflammatory biomarkers related to depression and CVD.

**Methods**

**Participants**

Forty-one undergraduates who were classified as being “physically fit” ($n = 21$, $M_{age} = 19.95 \pm 1.99$, Males = 17) or “physically unfit” ($n = 20$, $M_{age} = 20.35 \pm 1.84$, Males = 17) were recruited from seven sections of a health-related fitness course at a university in the southwest United States. The sample demographics (i.e., approximately 39% white, 29% Hispanic, 27% African-American, 3% Asian, and 3% mixed) were representative of all sections of the class. The university Institutional Review Board approved the study, and written informed consent was provided by all participants prior to data collection. Students had to meet both of the FitnessGram® standards (Plowman et al., 2006) for aerobic capacity (i.e., functional or physiological capacity to perform large-muscle activity for a prolonged period of time; Plowman & Meredith, 2013) and body composition (i.e., components that make up body weight, including fat, muscle, and bone content; Institute of Medicine, 2012) to be classified as physically fit. Specifically, females needed a $\text{VO}_{2\text{max}} \geq 38.6 \, \text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ and body fat percentage between 16.5-31.3%, and the males needed a $\text{VO}_{2\text{max}} \geq 44.3 \, \text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$.
and body fat percentage between 7.0-22.2%. Participants were classified as being physically unfit if they met both of these standards. Also, those who only met one of the standards did not qualify for this study. No one was excluded based on race or ethnicity, and all participants were between the ages of 18-25 years old to control for age (Howren et al., 2009). All females were eumenorrheic and not pregnant or trying to become pregnant.

Measures

Demographics. Participants self-reported their demographic information (i.e., gender, age, and ethnicity) and completed a medical history form. The form included whether they or close family members (e.g., parents) had ever been diagnosed with a physical (e.g., heart disease) or mental (e.g., depression) illness and whether they were currently using any tobacco, marijuana, or medications. Female participants also included their current use of birth control and date of last menses because these factors can influence levels of inflammation (Wander et al., 2008).

Body composition. The Omron HBF-360C Fat Loss Monitor was used as a noninvasive approach to measure body fat percentage through bioelectrical impedance (Ayvaz & Çimen, 2011). Evidence of concurrent validity has been found between this device and dual-energy, x-ray absorptiometry, or DEXA, for both men and women \( (r = .78, 74) \) with good repeatability \( (CV = 0.6\%); \) Jensky-Squires et al., 2008). Bioelectrical impedance was chosen because it can be used with FitnessGram standards (Plowman & Meredith, 2013), and it is a noninvasive, inexpensive, and quick method for large samples.
Progressive Aerobic Cardiovascular Endurance Run (PACER). The PACER is a progressive, multistage 20-meter shuttle run that provides an estimate of aerobic capacity (i.e., VO$_{2\text{max}}$). Previous research has found validity coefficients ranging from .83 to .93 when comparing the PACER to direct measures of VO$_{2\text{max}}$ and test-retest coefficients greater than .68 (Plowman & Meredith, 2013). Participants ran back and forth across a 20-meter distance as many times as possible while the pace got faster after each minute. The number of laps that each participant achieved was used to estimate VO$_{2\text{max}}$.

Muscular strength. Muscular strength was measured using the JAMAR hydraulic hand dynamometer, which is considered to be the gold standard for measuring handgrip strength (Roberts et al., 2011). Previous research has reported strong concurrent validity ($r = .99$) and strong reliability (ICC = .94; Mathiowetz, 2002). Participants held the dynamometer in their dominant hand while standing with their elbow extended and shoulder flexion at zero degrees. Maximal isometric contraction lasted for approximately three seconds. Peak handgrip strength was measured in pounds and converted to newtons to measure force. The handle was placed at the second position on the dynamometer because it has been found to provide the best estimates across a range of individuals (Trampisch, Franke, Jedamzik, Hinrichs, & Platen, 2012). However, bending the elbow or touching the dynamometer with the body during the isometric contraction was not allowed. Participants performed handgrip twice with the same hand after a two-minute break. Scores were rounded to the nearest pound and then converted to newtons as a measure of force. The highest of the two trials was used in the statistical analysis.
Muscular strength and endurance. It is difficult for fitness tests to measure only muscular endurance because muscular strength is usually being assessed at the same time (Haskell & Kiernan, 2000). Thus, three tests were used to assess muscular strength and endurance. First, participants completed the push-up test from the FitnessGram assessment to assess upper body strength and endurance (Plowman & Meredith, 2013). They completed as many repetitions as possible with good form at a cadence of approximately one push-up per three seconds. Previous research has found that approximately 64% and 76% of the variance was shared in male and female push-up and bench press scores, respectively (Plowman & Meredith, 2013). Second, the participants completed a cadence-based curl-up test (i.e., one curl-up per three seconds) to assess their abdominal strength and endurance. They completed as many curl-ups as possible while maintaining good form, and previous research has found reliability evidence for the curl-up test (Plowman & Meredith, 2013). Specifically, Robertson and Magnusdottir (1987) found a high degree of consistency ($r = .97$) among college students. Lastly, the horizontal plank test was also used because there are concerns that curl-ups requires a large amount of administrator training and subjective interpretation regarding proper form (Knudson, 1999). The horizontal plank test is easier to administer, requires fewer directions, and is more objective for the administrator than the curl-up test (Strand, Hjelm, Shoepe, & Fajardo, 2014). Participants supported themselves with only their forearms and toes in order to maintain this rigid body position as long as possible until failure from fatigue or poor form. Previous research has found test-retest correlations for the plank test to be .97 (Jernstedt, Saporito, Miller, & Coste, 2015).
Metabolic syndrome. The NCEP ATP III was used to measure metabolic syndrome, which requires at least three of the following to be present: (a) waist circumference > 102 cm in men and > 88 cm in women, (b) triglyceride level ≥ 150 mg/dL or currently being treated with drugs, (c) HDL < 40 mg/dL in men and < 50 mg/dL in women or currently being treated with drugs, (d) blood pressure ≥130/85 mmHg or currently being treated with drugs, and (e) fasting glucose ≥ 100 mg/dL or currently being treated with drugs (Grundy et al., 2005; National Cholesterol Education Program, 2002). Metabolic syndrome was used to find signs of CVD because previous research has found that metabolic syndrome is an important risk factor for CVD (Galassi et al., 2006). Serum samples were analyzed for triglycerides, HDL, and fasting glucose using enzymatic assays (Pointe Scientific, Canton, MI) and an automated chemistry analyzer (ChemWell-T, Awareness Technology, Inc. Palm City, FL).

Inflammatory biomarkers. Venous blood draws were used to collect serum samples and to measure concentrations of CRP, IL-6, IL-1β, and TNF-α. Serum samples of CRP were measured with a high-sensitivity ELISA from DRG International, INC. using a microplane spectrophotometer (PowerWave 340, Biotek, Inc. Winooski, VT). Concentrations of CRP were calculated using Gen5 software version 2.08 (Biotek, Inc. Winooski, VT). For IL-6, IL-1β, and TNF-α, supernatant was thawed and diluted (1:5) with assay buffer (MILLIPLEX MAP Assay Buffer, EMD Millipore, Billerica, MA). A commercially available human high-sensitivity cytokine assay (HSCYTMAG-60SK, EMD Millipore, Billerica, MA) was used with a Luminex-based system (Magpix, Luminex, Austin, TX) to measure the samples. MILLIPLEX® Analyst software (EMD Millipore, Billerica, MA) was used to measure concentration level. The intra-assay coefficients of
variation ranged from 13.1% to 18.7% for each analyte. All samples were measured in duplicates.

*Depression, Anxiety, and Stress Scales (DASS-21).* The DASS-21 (Antony et al., 1998) is a short form of the DASS (Lovibond & Lovibond, 1995) that measures negative affect over the past week. The DASS-21 was chosen because it is shorter than the original scale and has a stronger factor structure (Crawford et al., 2011; Henry & Crawford, 2005). Only the 14 items from the stress and depression subscales were used for the purpose of this study. The DASS-21 uses a 4-point Likert-type response scale from 0 (*Did not apply to me at all*) and 3 (*Applied to me very much, or most of the time*). Previous research with an adult population found Cronbach’s alpha to be .89 and .90 for the stress and depression subscales, respectively (Crawford et al., 2011). In addition, Cronbach’s alpha in the current study was .79 and .81 for the stress and depression subscales, respectively.

Procedures

At the beginning of each semester, all students from a health-related fitness course complete a series of fitness tests for aerobic capacity, body composition, and muscular strength and endurance and also the DASS-21. Prior to the fitness testing, students were recruited through a face-to-face class announcement for the opportunity to participate based on their fitness testing performance in the class. Students were told that they would receive a $50 gift card if they qualified and chose to participate. However, they were not told that they needed to achieve both or neither of the VO$_{2\text{max}}$ and body composition standards in order to qualify so that it would not influence their performance. Of the 251 students in the course, 190 (76%) signed up to participate.
After the fitness testing, they completed the stress and depression items from the DASS-21 online, but only 68 of those students met both or neither of the standards for VO$_{2\text{max}}$ and body composition. Text messages were then sent to contact these participants and schedule a time for them to complete the medical history form. After the forms were completed, 22 students were not able to participate for the following reasons: not responding to the text message, currently injured, scheduling conflicts, using tobacco products, taking anti-inflammatory medication, or taking birth control that drastically altered their menstrual cycle. This resulted in 46 participants being included in this study.

The participants arrived between 7 and 14 days after the fitness testing to receive the accelerometer. When they arrived, the participant’s blood pressure and waist circumference were measured. Blood pressure was measured based on guidelines set by the American Heart Association (Pickering et al., 2005) and waist circumference was measured to the closest one tenth of a centimeter. After these measurements were taken, the accelerometer was placed on their non-dominant wrist, and the participants were told to maintain their normal activity schedule for the next seven days. They received a daily log and were instructed to record when they slept and took off the accelerometer each day. They were also instructed to abstain from using tobacco, marijuana, or anti-inflammatory medication, and the participants also agreed to avoid exercising for 24 hours before the blood sample on the eighth day. However, five participants dropped out during the course of the study due to injury or sickness, which resulted in a final sample of 41 participants.
After wearing the accelerometers for eight days, the participants provided a blood sample between 8:00 am and 9:20 am after an overnight fast. To control for menstrual cycle, all blood samples for females were collected 7 to 14 days after their last menses (Wander et al., 2008). Prior to the blood sample, participants sat quietly for at least 10 minutes to control for plasma volume shifts. Trained technicians collected approximately 18 mL of blood using sterile technique. After allowing the samples to clot for 20 minutes, they were centrifuged for 20 minutes at 1500g at 4°C. The serum samples were aliquoted and stored at -80°C Celsius until they were thawed for analysis.

Statistical Analysis

Data was managed and analyzed using SPSS version 22. First, the following were examined during the preliminary analysis: skewness for all variables; means, standard deviations, and correlations for amount of PA, physical fitness scores, biomarker concentrations, and the DASS-21 scores; and assessing the internal consistency of the DASS-21 subscales. The level of significance for all tests was set at .05.

Biomarkers. Second, two descriptive discriminant analysis were conducted to determine whether differences existed in the dependent variables (i.e., biomarkers for metabolic syndrome and inflammation) as a function of the independent variable (i.e., fitness group). Compared to the physically unfit group, it was hypothesized that the physically fit group would have lower scores related to waist circumference, blood pressure, triglycerides, fasting glucose, and cytokines but higher scores related to HDL. Third, two canonical correlations were conducted between a composite of the HRF variables with a composite of the metabolic syndrome variables and also a composite of
the inflammatory biomarkers. This was used to determine which aspects of HRF accounted for the most variance in the biomarkers. It was hypothesized that aerobic capacity and body fat percentage would account for more variance in the biomarkers than the muscular strength and endurance tests.

Self-reported depression and stress. Fourth, a t-test was conducted to investigate the difference between those classified as physically fit or unfit on their self-reported scores for stress and depression. The physically fit participants were expected to have lower mean scores for depression and stress. A priori power analysis indicated that an effect size of .80 would achieve a power .80 with a sample size of 41. Lastly, to determine which aspects of HRF account for the most variance in the stress and depression scores, a canonical correlation was conducted to compare the composite of the HRF variables with the stress and depression scores. Similar to the biomarkers, aerobic capacity and body fat percentage were expected to account for more of the variance than the muscular strength and endurance tests.

Results

Descriptive Statistics

Table 1 includes the descriptive statistics for HRF (i.e., body composition, VO2max, push-ups, curl-ups, plank, and handgrip), metabolic syndrome (i.e., waist circumference, triglycerides, HDL, blood pressure, and fasting glucose), CRP, cytokines (i.e., IL-6, IL-1β, and TNF-α), and the depression and stress subscales from the DASS-21. Pearson r correlations can be found in Table 2. For example, a statistically significant negative correlation was found between VO2max and CRP (r = -.62) and also IL-6 (r = -.46). In addition, correlations ranged from -.71 to .70 for the HRF variables,
from -.32 to .50 for the PA variables, from -.60 to .54 for the metabolic syndrome variables, and from -.33 to .72 for the inflammatory biomarkers. After examining the skewness for all variables, a Box-Cox transformation was conducted for variables with a skewness greater than .80 or less than -.80. This included the following variables: push-up, plank, waist measurement, triglycerides, glucose, HDL, CRP, IL-6, IL-1β, TNF-α, depression, and stress. Thus, after using a λ between -2.0 and 1.8, the transformation resulted in a range of skewness from -.07 to .12.

Based on the medical history form, 20% of the participants had at least one immediate family member (i.e., parents, siblings, or grandparent) with heart disease, 54% with diabetes, 17% with stroke, 46% with high blood pressure, and 20% with high cholesterol or triglycerides. In addition, 10%, 7%, and 10% of participants reported that an immediate family member had been diagnosed with anxiety, depression, or other mental illness, respectively. In regards to the participants, 7% self-reported that they had been diagnosed with high blood pressure, 2% with high cholesterol or triglycerides, 5% with low HDL, 7% with anxiety, and 5% with depression. However, the results of this study indicated that 80% of the physically unfit participants exhibited at least two symptoms for metabolic syndrome, and 44% of those met the requirement for a minimum of three symptoms to qualify for metabolic syndrome. Specifically, 33% of the physically unfit participants had high waist circumference, 33% high systolic or diastolic blood pressure, 0% high triglycerides, 45% low HDL, and 3% high glucose. This indicated that there were some differences between the self-reported and measured biomarkers for metabolic syndrome.

Primary Statistics
Biomarkers. First, two descriptive discriminant analyses were conducted to determine which biomarkers for metabolic syndrome and inflammation accounted for group differences between physically fit and physically unfit participants. The full model for metabolic syndrome and fitness group was statistically significant, Wilks’ $\lambda = .29$, $\chi^2(6) = 44.77$, $p < .001$, and the squared canonical correlation was .71. This indicated that the fitness group variable explained 71% of the differences in the metabolic syndrome composite. Group differences were determined using structure coefficients ($r_s$, i.e., correlation between each dependent variable and the composite) and standardized coefficients (i.e., relative importance of each dependent variable in the model), which are in Table 4. Group differences were primarily due to waist circumference ($r_s = .85$), triglycerides ($r_s = .37$), diastolic blood pressure ($r_s = .31$), and HDL ($r_s = -.44$). The remaining variables each explained less than 5% of the group differences in the composite for the metabolic syndrome and were not considered to have contributed to group differences. The group centroids (i.e., the mean of each group on the composite) were also examined to investigate whether a statistically significant difference existed across groups on the composite. The group centroid for physically unfit students was significantly higher than those considered to be physically fit ($p < .001$, Cohen’s $d = 3.16f$). Specifically, the higher group centroid for the physically unfit group was related to primarily higher waist circumference, triglycerides, and diastolic blood pressure and also lower HDL.

The full model for inflammatory biomarkers and fitness group was not statistically significant, Wilks’ $\lambda = .78$, $\chi^2(4) = 9.05$, $p = .06$, but yielded a squared canonical correlation of .22. Because this indicated that 22% of the variance in the inflammatory
biomarkers was explained by fitness group (i.e., inverse of Wilks’ $\lambda$), the model was considered statistically meaningful. These group differences were primarily due to CRP ($r_s = .55$) and TNF-$\alpha$ ($r_s = .28$). A $r_s$ of approximately .3 (i.e., about 9% of variance explained) has been suggested by previous research as a cutoff for determining which variables contribute to group differences (Enders, 2003). IL-1$\beta$ and IL-6 accounted for less than 3% of the variance in the inflammatory biomarker composite so they were not considered to have contributed to group differences. However, there was evidence that TNF-$\alpha$ and IL-6 acted as a suppressor variables due to their large standardized coefficients and low structure coefficients. TNF-$\alpha$ and IL-6 were credited with larger standardized coefficients (.92 and -.83, respectively) because they explained variance in the other inflammatory biomarkers and improved the overall model fit even though these variables were not strongly related to the composite ($r_s^2 = .28$ and .02, respectively). For example, in the physically unfit group, IL-6 was significantly correlated to CRP ($r = .50, p < .01$) and TNF-$\alpha$ ($r = .68, p < .01$). The group centroids for physically unfit students was significantly higher than those considered to be physically fit ($p < .001, $Cohen’s $d = 1.03$). Specifically, the higher group centroid for the physically unfit group was related to primarily higher concentrations of CRP and TNF-$\alpha$.

Next, two canonical correlations were conducted with all the participants to investigate the relationship between HRF and two types of biomarkers (i.e., metabolic syndrome and inflammation). The standardized canonical function coefficients and structure coefficients for the criterion and predictor variables from each canonical correlation can be found in Table 5. The first canonical correlation associating HRF with the metabolic syndrome variables indicated that only the first function was statistically
significant with 89% of the variance was shared between both sets of variables (i.e., inverse of Wilks’ $\lambda$), Wilks’ $\lambda = .11$, $F(36, 130.11) = 2.34, p < .001$. The squared canonical correlation for the full model was .79. Based on the structure coefficients, the metabolic syndrome composite was primarily composed of waist circumference ($r_s = -.99$), triglycerides ($r_s = -.49$), glucose ($r_s = -.47$) and HDL ($r_s = .56$), whereas the HRF composite largely consisted of body fat percentage ($r_s = -.66$), VO$_{2\text{max}}$ ($r_s = .71$), number of curl-ups ($r_s = .76$), amount of force generated for handgrip strength ($r_s = -.53$), and performance on plank test ($r_s = .68$). The squared canonical index (i.e., amount of variance shared by each variable with the other canonical variate) supported these findings by multiplying each structure coefficient with the overall canonical correlation. Specifically, the HRF variables explained between 13 – 40% of the variance in the metabolic syndrome composite, and 5 – 77% of the variance in HRF could be explained by the metabolic syndrome variables. The second canonical correlation associating HRF with the inflammatory biomarkers was not statistically significant, Wilks’ $\lambda = .45$, $F(24, 109.36) = .99, p = .49$, but 55% of the variance was shared between both sets of variables. This indicated that a larger sample size would be needed to find statistical significance.

**Self-reported depression and stress.** Lastly, to compare group differences on the depression and stress subscales of the DASS-21, an independent samples $t$ test was conducted. After checking equality of variances for depression ($p = .52$) and stress ($p = .49$), the $t$ test yielded a nonsignificant difference between the physically fit and physically unfit groups for depression, $t(39) = -1.39, p = .17$, Cohen’s $d = .43$ and stress, $t(39) = -1.29, p = .20$, Cohen’s $d = .40$. A canonical correlation associating HRF with the
depression and stress variables was also not statistically significant, Wilks' $\lambda = .59$, $F(12, 66) = 1.64, p = .10$, but 41% of variance was shared between both sets of variables. Thus, because though a moderate effect size was found for depression and stress and for the relationship between HRF and depression and stress, this indicated that a larger sample size might be needed to find statistical significance.

**Discussion**

The purpose of the current study was to investigate the role of different aspects of HRF with biomarkers for depression and CVD (i.e., proinflammatory biomarkers and metabolic syndrome). The results indicated that the group differences for metabolic syndrome were primarily due to the physically unfit group having higher waist circumference, diastolic blood pressure, triglycerides, and lower HDL than the physically fit group. The relation between the individual aspects of HRF and metabolic syndrome was also investigated. Specifically, having a lower body fat percentage and handgrip strength and performing better on the $VO_{2\text{max}}$, curl-ups, and plank tests were associated with a smaller waist circumference, lower concentrations of triglycerides and glucose, and higher concentrations of HDL. A weaker handgrip strength was related to a healthier CVD profile due the physical characteristics of the participants. The physically unfit participants could generate higher muscular strength scores likely due to their larger body mass, whereas the physically fit group tended to be leaner and more aerobically trained.

Furthermore, in regards to the proinflammatory biomarkers, group differences were primarily due to the physically unfit group having higher concentrations of CRP and TNF-$\alpha$ than the physically fit group, whereas IL-6 acted primarily as a suppressor.
variable due to its significant correlation with these variables. The canonical correlation between HRF and proinflammatory biomarkers was not statistically significant, but the large amount of shared variance indicated that a larger sample size might be needed to find statistical significance, even though lower body fat percentage and handgrip strength and performing better on the VO\textsubscript{2max}, curl-ups, and plank tests was associated with lower concentrations of CRP. This provided initial support that similar aspects of HRF were related to a healthier profile for metabolic syndrome and inflammation. In addition, a small-to-moderate effect size was found between the physically fit and physically unfit participants on their self-reported depression and stress.

In regards to the benefits of improving different aspects of HRF on health outcomes, a large focus has been placed on the importance of either cardiorespiratory fitness or body fat percentage. For example, Lee, Jackson, and Blair (1998) analyzed data from 21,925 men over an eight-year period from the Aerobic Center Longitudinal Study. Each participant completed a maximal treadmill exercise test and a body composition assessment as part of a complete preventative medicine examination. After adjusting for age, examination year, cigarette smoking and alcohol intake, the authors found that the relative risk for all-cause mortality was lower in fat but fit men compared those who were lean but unfit. This provided initial evidence that the negative health consequences of excess adiposity might be reversed by improving cardiorespiratory fitness or that fitness might be beneficial even in the absence of weight loss (Hainer, Toplak, & Stich, 2009).

In addition, Janssen and Cramp (2007) conducted a cross-sectional study with a national representative sample of 1,561 adolescents from the National Health and
Nutrition Examination Survey 1999-2002. The purpose of their study was to examine the relation between cardiorespiratory fitness and metabolic syndrome and to determine whether this relationship was consistent across sex and ethnicity. They found that higher levels of CRF was associated with lower odd ratios for each aspect of metabolic syndrome (i.e., high waist circumference, blood pressure, triglycerides, glucose, and low HDL) across sex and ethnicity. These findings were supported by a more recent study conducted by Lee and colleagues (2005) who found that higher levels of cardiorespiratory fitness were associated with lower health risks for metabolic syndrome across different levels of visceral and subcutaneous fat. However, other studies indicated that body fat is more important for health outcomes. For example, Christou et al. (2005) found that body fatness (i.e., BMI, percent body fat, and waist circumference) was a better predictor of CVD risk factors than cardiorespiratory fitness in 135 healthy men across a range of metabolic, hemodynamic, and hemostatic risk factors. Thus, it is important to consider that both determinants are interrelated due to the positive relationship between PA and fitness and the negative relationship between PA and fatness (Hainer et al., 2009). Furthermore, the results of the current study indicated that other aspects of HRF (e.g., muscular strength and endurance) might also be important to consider. In addition to VO_{2\text{max}} and body composition, the participant’s performance on the handgrip, curl-up, push-up, and plank tests contributed to group differences on the biomarkers for metabolic syndrome.

In regards to inflammatory biomarkers, a number of studies have investigated the effect of PA and exercise interventions (Glynn et al., 2007), but more information is still needed regarding the role of physical fitness (Buchan et al., 2012). Previous research
indicates that VO\textsubscript{2max} is negatively associated with CRP and IL-6 (e.g., (Aronson et al., 2004; Kullo, Khaleghi, & Hensrud, 2007), which is supported by the findings of the current study. Specifically, the physically fit group, which had higher levels of VO\textsubscript{2max} and lower body fat percentage, had lower concentrations of CRP and TNF-\(\alpha\) compared to physically unfit group. In addition, Casey (2013) conducted a study with 96 participants who were enrolled in phase-II cardiac rehabilitation to investigate the relationship between physical fitness with depression and inflammation. Physical fitness was measured using a treadmill exercise test, and she reported that physical fitness moderated the relationship between depression and IL-6. Specifically, a positive relationship between depression and IL-6 was found for those with lower levels of physical fitness. In addition, Ruiz and colleagues (2007) conducted a study with 142 children aged 9-10 years old. They reported that low-grade proinflammatory markers were negatively related to cardiorespiratory fitness and positively related to fatness (i.e., skinfold thickness). They reported that the role of fatness was slightly stronger than cardiorespiratory fitness, whereas the current study indicates that cardiorespiratory fitness had a stronger relationship with CRP and TNF-\(\alpha\) than fatness. This highlights how the relative importance of fitness and fatness may change across different studies.

Thus, due to some slightly inconsistent findings, it is important to remember that physical fitness incorporates a set of attributes and is an integrated measure that includes many bodily systems (e.g., skeletomuscular and cardiorespiratory; Caspersen et al., 1985; Ortega, Ruiz, Castillo, & Sjöström, 2008). After searching previous literature, this appears to be the first study that investigated the role of several aspects of HRF with biomarkers for metabolic syndrome and inflammation. However, it is
important to remember that the purpose of this study was not to highlight the importance of a single aspect of HRF. Instead, it was hypothesized that each aspect of HRF may contribute to fitness group differences. The results indicated that the participant’s performance on the muscular strength and endurance tests was related to group differences on the metabolic syndrome and proinflammatory biomarkers. Thus, it might be beneficial for future research to incorporate several aspects of HRF when investigating the relationship between mental and physical health.

There were several strengths associated with the current study. First, objective measures for HRF, CVD, and mental health were collected using the FitnessGram assessments, metabolic syndrome variables, and inflammatory biomarkers. Specifically for CVD and mental health, these measures reduced many of the common limitations associated with self-report measures, such as social desirability bias and incorrect recall. Second, to account for possible confounding variables, the following factors were controlled by the design of the current study: age, smoking and alcohol behaviors, exercising within 24 hours of the blood sample, menstrual cycle, anti-inflammatory medications, sickness, and injury. Controlling these variables limited their effect on the results of the current study. Third, a sample of physically fit and physically unfit students were recruited to create greater differences between the groups. This difference was created by using two HRF measures (i.e., aerobic capacity and body composition) to determine if each participant met the criterion-referenced standards for each HRF measure.

Despite the strengths of this study, there are several limitations to consider. First, the sample size was limited due to the costs associated with analyzing the biomarkers.
Only students who met both or neither of the criterion-referenced standards for aerobic capacity and body composition were eligible to participate. This improved statistical power by creating greater differences between the two fitness groups. However, the lack of statistical significance in some cases, even when the results yielded moderate effect sizes, indicated that larger samples sizes might be needed in future research.

Second, one of the limitations of the DASS-21 is that the self-report questionnaire is susceptible to social-desirability bias. This may have affected the results if some of the participants chose to report that they had a more positive mental health profile. It is also important to remember that the current sample did not include individuals reporting clinical symptoms of depression. Thus, additional research is needed with samples experiencing more severe and chronic symptoms of depression and stress.

Third, it is possible that not all students were fully motivated to provide maximum effort during the fitness testing. To address this issue, the fitness testing in each class was administered by the lead investigator, and regular feedback and encouragement was provided to ensure that the testing environment was consistent across all the classes. Future research is needed to examine student motivation during fitness testing moderates the relationships between HRF and the biomarkers. Fourth, even though the physically fit group engaged in more PA than the unfit group, the participants in the current study were generally physically active because they were recruited from a health-related fitness class. Future research might find additional differences when comparing physically active and sedentary groups. Lastly, the measures in the current study were not direct measures of depression and CVD, but they are related to preventative risk factors associated with these diseases.
Conclusion

The results of the current study indicated that group differences between physically fit and physically unfit young adults for both metabolic syndrome and proinflammatory biomarkers were primarily due to the same aspects of HRF. Specifically, the physically fit group had lower body fat percentage and handgrip strength and higher levels of VO$_{2\text{max}}$, curl-ups, and plank. These variables were related to a healthier profile for metabolic syndrome (i.e., smaller waist circumference, lower triglycerides and glucose, higher HDL) and inflammation (i.e., lower CRP) than the physically unfit group. In addition, a small-to-moderate effect size was found between the physically fit and unfit participants on their self-reported depression and stress. While the current study included participants diagnosed with metabolic syndrome, future research should investigate if these aspects of HRF are related to biomarkers for metabolic syndrome and depression in clinical samples who are experiencing more severe psychological disorders.
References


Institute of Medicine. (2012). *Fitness measures and health outcomes in youth*. Washington, D.C.


Table 1
Descriptive Statistics for Physical Fitness, Physical Activity, Metabolic Syndrome, Inflammatory Biomarkers, and DASS-21 Subscales

<table>
<thead>
<tr>
<th>Variable</th>
<th>Physically Fit M</th>
<th>SD</th>
<th>Physically Unfit M</th>
<th>SD</th>
<th>p</th>
<th>Cohen’s d</th>
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<td>2. VO(_{2\max})</td>
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<td>.22</td>
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<td>4. Curl-ups</td>
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<td>5. Plank (seconds)</td>
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<td>98.25</td>
<td>40.43</td>
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<td>6. Handgrip (N)</td>
<td>439.31</td>
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<td>493.31</td>
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<td>76.66</td>
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<td>17. IL-6 (pg/ml)</td>
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<td>19. TNF-(\alpha) (pg/ml)</td>
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*Note. N = newtons; BP = blood pressure; HDL = high-density lipoprotein; CRP = C-reactive protein; IL-6 = interleukin-6; IL-1\(\beta\) = interleukin-1\(\beta\); TNF-\(\alpha\) = tumor necrosis factor-\(\alpha\).*
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**Note.** Mod = moderate; Vig = vigorous; BP = blood pressure; HDL = high-density lipoprotein; CRP = C-reactive protein; IL-6 = interleukin-6; IL-1β = interleukin-1β; TNF-α = tumor necrosis factor-α.

*<p < .05. **<p < .01.
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*Note. MVPA = moderate and vigorous physical activity; HDL = high-density lipoprotein; $B$ = unstandardized regression coefficients; $r_s$ = structure coefficients.

*p < .05. **p < .01.
Table 4

**Descriptive Discriminant Analyses and Group Centroids for Synthetic Composite for Biomarkers**

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<th>$r^2_s$</th>
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*Note. BP = blood pressure; HDL = high-density lipoprotein; CRP = C-reactive protein; IL-6 = interleukin-6; IL-1\(^β\) = interleukin-1\(^β\); TNF-\(α\) = tumor necrosis factor-\(α\). $r_s$ = Structure coefficients; $r^2_s$ = Squared structure coefficients; $R^2_c$ = Squared canonical correlation. \(^a\)Met the approximate |.3| minimum for interpretability (Enders, 2003).*
Table 5

| Standardized Canonical Function Coefficient and Structure Coefficients for Canonical Correlation |
|---------------------------------------------------------------|----------------------|----------------------|
|                                                               | Standardized Coefficient | $r_s$ | $r_s^2$ | Squared Canonical Index |
| First Canonical Correlation $^a$                              | Health-related Fitness  |                      |         |                       |
| VO$_{2max}$                                                   | .05                   | .71      | .51     | .40                    |
| Body Fat %                                                    | -.34                  | -.66     | .44     | .34                    |
| Curl-ups                                                     | .42                   | .76      | .58     | .45                    |
| Push-ups                                                     | -.09                  | .40      | .16     | .13                    |
| Handgrip                                                     | -.54                  | -.53     | .28     | .22                    |
| Plank                                                        | .25                   | .68      | .46     | .36                    |
| Metabolic Syndrome                                           | Waist                 | -.98     | -.99    | .98                    | .77  |
| Systolic BP                                                  | -.04                  | -.26     | .07     | .05                    |
| Diastolic BP                                                 | .05                   | -.38     | .14     | .11                    |
| Triglycerides                                                | .03                   | -.49     | .24     | .19                    |
| Glucose                                                      | -.13                  | -.47     | .22     | .17                    |
| HDL                                                          | -.03                  | .56      | .31     | .25                    |
| Second Canonical Correlation $^b$                             | Health-related Fitness|                      |         |                       |
| VO$_{2max}$                                                   | 1.42                  | .84      | .70     | .27                    |
| Body Fat %                                                    | .75                   | -.55     | .30     | .11                    |
| Curl-ups                                                     | .27                   | .54      | .30     | .11                    |
| Push-ups                                                     | .09                   | .39      | .16     | .06                    |
| Handgrip                                                     | -.30                  | -.45     | .20     | .08                    |
| Plank                                                        | -.20                  | .45      | .21     | .08                    |
| Proinflammatory Biomarkers                                   | CRP                   | -1.02    | -.98    | .96                    | .36  |
| IL-6                                                         | .15                   | -.31     | .10     | .04                    |
| IL-1$\beta$                                                  | -.04                  | .14      | .02     | .01                    |
| TNF-$\alpha$                                                 | -.25                  | -.21     | .04     | .02                    |

Note. BP = blood pressure; HDL = high-density lipoprotein; CRP = C-reactive protein; IL-6 = interleukin-6; IL-1$\beta$ = interleukin-1$\beta$; TNF-$\alpha$ = tumor necrosis factor-$\alpha$; Standardized Coefficient = Standardized canonical function coefficient; $r_s$ = structure coefficient; $r_s^2$ = squared structure coefficient.

$^a_r_s^2 = .79$. $^b_r_s^2 = .38$. 

68
APPENDIX

EXTENDED LITERATURE REVIEW
As a growing number of youth enroll in postsecondary institutions, emerging adulthood (i.e., 18-25 years old) has received increased attention in industrialized countries as an important transitional period for developing healthy behaviors and disease prevention (Arnett, 2000; Bureau of Labor Statistics, 2015; Nelson et al., 2008). Arnett (2000) first described this period as “emerging adulthood”, which is characterized by relative independence from social roles and from normative expectations. Emerging adults do not depend on their parents as much as adolescents, but they still have not acquired all of the responsibilities of adulthood. The challenges that emerging adults face differ from late adulthood because many of them are adjusting to living away from parents for the first time, earning an education, entering the workforce, and trying to find a life partner (Arnett, Žukauskiene, & Sugimura, 2014). While many emerging adults do not view themselves as adolescents or adults (Arnett, 2000), these developmental differences are not always recognized. Instead, it is common for emerging adulthood to be included with either adolescence or middle-adulthood (Arnett, Žukauskienė, & Sugimura, 2014). Emerging adulthood has gradually received more attention since Arnett’s (2000) original paper because of the mental (e.g., depression) and physical (e.g., cardiovascular disease [CVD]) health issues that can arise during this time (Tanner & Arnett, 2013).

In recent years, a growing number of young adults have experienced mental health problems, such as depression (Eisenberg et al., 2013; Gallagher, 2014; Twenge et al., 2010). They regularly face many stressful situations (e.g., due to academic pressure, loneliness, and financial obligations; Eisenberg et al., 2013; Nelson et al.,
and prolonged stress can increase their risk for developing depression (Eyre & Baune, 2012). In addition, young adults are at greater risk for developing CVD because the prevalence of obesity has more than doubled over the past 30 years in this age group (Nelson et al., 2008). Furthermore, depression and CVD are projected to be the two largest causes of years lost due to ill-health, disability, or early death for all ages by 2020 (Reddy, 2010), and these health issues are related (i.e., depression can lead to CVD and vice versa; Blaine, 2008; Huffman et al., 2013; Van der Kooy et al., 2007). Thus, establishing effective and efficient methods to measure the severity of depression and CVD at an earlier age may help prevent or reduce the personal, social, and economic burden associated with these diseases (Buchan et al., 2011).

Depression

Depression is recognized as one of the most prevalent types of mood disorders today (Blumethal et al., 2005), especially for young adults in the United States (Eisenberg, Gollust, Golberstein, & Hefner, 2007; Eisenberg et al., 2013; Twenge et al., 2010). For example, Gallagher (2014) surveyed the directors of college counseling centers across the United States and Canada, and approximately 58% of the directors reported an increase over the past five years of clinical depression. Current estimates also indicate that 17% of the United State population (between 5-12% of men and 10-20% of women) will experience a major depressive episode at least once in their lifetime (Blumethal et al., 2005; Kessler et al., 2005). Thus, an important step in preventing or reducing the burden of depression is to develop effective and efficient methods for identifying individuals who are at-risk or currently experiencing symptoms of depression.
Self-report questionnaires are regularly used to identify depression because they are inexpensive, easy to administer, and can provide an initial assessment of those who might be at-risk for depression. One popular questionnaire is the Depression Anxiety Stress Scales (DASS; Lovibond & Lovibond, 1995). The DASS includes items that measure depression, anxiety, and stress. While the DASS is not intended to diagnose depression, it does include thresholds for normal, moderate, and severe labels. The original scale had 42 items, but the psychometric properties of a shortened version with 21 items (DASS-21) have been supported (Henry & Crawford, 2005; Sinclair et al., 2012). The DASS-21 has been found to have good internal consistency, strong convergent validity with other anxiety and depression measures, and high sensitivity to changes in depression with healthy and clinical samples (Henry & Crawford, 2005; Weiss, Aderka, Lee, Beard, & Björgvinsson, 2015).

To diagnose depression, clinicians also use clinical interviews and the 5th edition of the Diagnostic and Statistical Manual (DSM-5), which is the most widely accepted guide for classifying psychiatric and psychological disorders. Using all three methods (i.e., self-report, interviews, and the DSM-5) can help clinicians examine depression from multiple perspectives to ensure that the diagnosis is correct. However, there is an ongoing debate about the objectivity of this approach (Lopresti et al., 2014). Due to the heterogeneous nature of depression, it can be difficult to diagnose in real-world settings, which can delay possible treatment and lead to poorer outcomes (Carvalho et al., 2014; Schmidt et al., 2011). One option that has been suggested to aid in this process is the use of biomarkers (i.e., indicators of normal, pathogenic, or pharmacological processes that can be measured objectively; Lopresti et al., 2014).
Similar to how genetics tests are conducted to identify possible illnesses later in life, biomarkers can potentially help clinicians understand the biological causes of depression. Using biomarkers as another diagnostic tool could overcome the limitations of only using subjective assessments. In fact, biomarkers for other diseases have been used to successfully diagnose illness, predict treatment, measure treatment progress, and predict future onset (Lopresti et al., 2014). While previous research has tried to identify a single biomarker that would diagnose depression, these attempts have not been successful due to the heterogeneous nature of depression (Rao, 2013). Despite these difficulties, there is evidence that a panel of biomarkers could be used to identify the presence or absence of depression (Schmidt et al., 2011).

Proinflammatory biomarkers (e.g., CRP, IL-6, IL-1β, and TNF-α) are one of the most common types of biomarkers used to assess depression. Previous research has indicated that each of these biomarkers is positively related to depression symptoms (Eyre et al., 2013; Hamer & Stamatakis, 2010; Lopresti et al., 2014; Müller et al., 2011; Rao, 2013). For example, Howren and colleagues (2009) conducted a meta-analysis with 136 studies to investigate the relation between depression and proinflammatory biomarkers (i.e., CRP, IL-6, and IL-1β). The authors reported that there was a statistically significant positive relationship among these variables. This association existed across clinical and community adult populations and also for studies that used clinician interviews or self-report measures of depression. Furthermore, a more recent meta-analysis by Haapakoski and Alenius (2015) reported that depression was positively related to CRP, IL-6, IL-1β, and TNF-α. These associations existed even
though the strength of the relationships varied based on the method used to diagnose depression, the sample characteristics, and potential confounders.

One possible explanation for this positive association between depression and proinflammatory biomarkers is through the bidirectional relationship between the central nervous system and the immunity system (Howren et al., 2009). Inflammation increases in response to decreased parasympathetic activity, which is associated with increases in depression (Kop & Gottdiener, 2005). This increase in inflammation and higher concentrations of proinflammatory biomarkers leads to increased activity in the hypothalamic-pituitary-adrenal (HPA) axis by releasing corticotrophin-releasing hormone and cortisol, which can initiate or worsen depressive symptoms. Stress can also play a role in depression by increasing the activity of the HPA axis (Stepanichev et al., 2014). Prolonged exposure to these stressors can increase a person’s risk for developing depression due to the stress-induced production of proinflammatory biomarkers (Eyre & Baune, 2012; Stepanichev et al., 2014). For example, previous research has indicated that the acute administration of IL-6, IL-1β, and TNF-α can result in a group of symptoms known as “sickness behaviors”, such as anhedonia, fever, sleep changes, and decreased social interaction (Dantzer, Connor, Freund, Johnson, & Kelley, 2008). Similarities between these symptoms and depression has led to the proposal of the cytokine hypothesis for depression. The cytokine hypothesis postulates that an increase in proinflammatory biomarkers can signal the brain to adopt these sickness behaviors. An increase in concentration of these biomarkers may play a role in the pathology of depression because they positively correlate with the severity of depression (Schiepers et al., 2005).
CVD

As the leading cause of mortality worldwide, there is also a continued need to understand the risk factors associated with CVD. The World Health Organization estimated that 17.5 million people died from CVD worldwide in 2012, and approximately one in four deaths in the United States are due to CVD (Centers for Disease Control and Prevention, 2015; World Health Organization, 2014). Although the process is quite complex, there is evidence that immune pathways and inflammatory processes contribute to the development of CVD through atherosclerosis. Atherosclerosis is the deposit of plaque in blood vessels that limits the supply of blood and oxygen to the heart (Shrivastava et al., 2014). It is characterized by low-grade inflammation that affects the endothelium of the arteries (Shrivastava et al., 2014). In addition, there is an increase in the concentration of proinflammatory biomarkers, such as acute-phase proteins (e.g., CRP) and cytokines (e.g., IL-6, IL-1β, and TNF-α), that can destabilize plaque and lead to cardiovascular events (Libby, 2012).

While it has traditionally been associated with adulthood, more risk factors associated with CVD (e.g., obesity and metabolic syndrome) are beginning to appear in childhood or adolescence and can persist through the lifespan into adulthood (Buchan, Ollis, Thomas, Malina, & Baker, 2011; Saland, 2007). For example, the transitioning from adolescence and adulthood has been identified as a period of heightened risk for weight gain, especially for college students (Nelson, Story, Larson, Neumark-Sztainer, & Lyle, 2008). Levitksy and colleagues (2004) found that the average weight gain for freshmen was 4.1 ± 5.29 pounds after the first 12 weeks of the semester. Anderson, Shapiro, and Lindgren (2003) found similar results with 25% of college freshman...
gaining at least five pounds after the fall semester, and the number of overweight and obese participants doubling by the end of the first school year. Emerging adulthood may be an important time for establishing a healthy lifestyle because unhealthy behaviors during this period are associated with higher risk for chronic diseases, such as CVD. Therefore, Buchan and colleagues (2011) highlighted the need to identify risk factors for CVD as early as possible. Otherwise, an unhealthy CVD profile may lead to issues later in adulthood.

Like depression, the etiology of CVD is complex and can include a wide range of risk factors (e.g., metabolic syndrome, lack of PA, low aerobic fitness, and genetics), but unlike depression, multiple biomarkers currently exist to measure a person’s risk for developing CVD. One important set of biomarkers for CVD is metabolic syndrome (Galassi et al., 2006). Based on the National Cholesterol Education Program’s Adult Treatment Panel-III (ATP III; National Cholesterol Education Program, 2002), metabolic syndrome can be diagnosed by having three or more of the following five indicators: high waist circumference, high triglycerides, high blood pressure, high fasting glucose, and low HDL. Due to the relation between metabolic syndrome and CVD, these indicators can be used to estimate a person’s CVD profile (Galassi et al., 2006). For example, a meta-analysis by Galassi and colleagues (2006) found that metabolic syndrome increased the risk of CVD by 61%. They reported that metabolic syndrome led to increased mortality from all causes and CVD and increased incidence of CVD, coronary heart disease, and stroke.

Even though important risk factors associated with CVD have been identified, approximately 50% of CVD events occur in individuals who have few or no signs of the
traditional risk factors (Shrivastava et al., 2014). As a result, additional research has investigated whether other biomarkers might help identify signs of CVD. One pathway that has been suggested is through proinflammatory biomarkers because increases in inflammation is central to CVD risk (Buchan et al., 2012). For example, higher concentrations of CRP have been found in people with individual symptoms of metabolic syndrome (e.g., overweight or hypertriglyceridemia; Ridker et al., 2003) and those without overt signs of CVD (Lee et al., 2004). This association is possibly related to having excess fat tissue because CRP is synthesized by adipocytes, even though it is primarily produced in the liver in response to IL-6 (Fain, 2006). CRP has also been identified by the Centers for Disease Control and Prevention and the American Heart Association as an independent marker and predictor of CVD due to its role in atherosclerosis and inflammation. Thus, CRP and other proinflammatory biomarkers (e.g., IL-6, IL-1β, and TNF-α) may add clinically important information to metabolic syndrome and improve CVD risk assessment (Ridker et al., 2003).

Because low-grade, chronic inflammation is a common characteristic of both depression and CVD (Buchan et al., 2012; Müller et al., 2011), previous research has indicated that these disease are interrelated (i.e., CVD can lead to depression and vice versa; Blaine, 2008; Buchan et al., 2011; Buchan, Thomas, et al., 2012; Glynn et al., 2007; Huffman et al., 2013; Müller et al., 2011; Van der Kooy et al., 2007). For example, rates of depression are higher in cardiac patients than the general population, and depression is also an independent risk factor for cardiac morbidity and mortality (Huffman et al., 2013; Peterson et al., 2002). Approximately 31-45% of patients with CVD have reported experiencing clinically significant symptoms of depression (Celano
& Huffman, 2011). Furthermore, Blaine (2008) conducted a meta-analysis on 16 longitudinal studies to investigate the causal effects of depression on obesity. Each study included a baseline measure of depression and a follow-up measure of weight change. Odds ratio were used to estimate the probability of depressed participants having obesity status or weight gain at follow-up compared to non-depressed participants. Blaine (2008) reported that depressed participants had a significantly higher risk for developing obesity. Specifically, an odds ratio of 1.47 (95% CI: 1.16, 1.85) indicated that individuals who were depressed at baseline were 47% more likely than those without depression to be obese or experience weight gain by the end of the study. One explanation for this relationship is due to the similarities between the correlates of depression and immune systems risk factors for CVD (e.g., higher concentrations of CRP and cytokines; Adibfar, Saleem, Lanctôt, & Herrmann, 2016; Kop & Gottdiener, 2005). Thus, measuring proinflammatory biomarkers could provide information about the ability of regular PA or improving physical fitness to decrease chronic inflammation.

Role of PA with Depression and CVD

One important option for decreasing inflammation in both depression and CVD is regular PA (i.e., any bodily movement produced by skeletal muscles that results in energy expenditure; Caspersen, Powell, & Christenson, 1985). Regarding depression, previous research has generally found a negative association between PA and symptoms of depression. Mammen and Faulkner (2013) conducted a systematic review of 30 longitudinal studies, and 25 of the studies reported a negative relationship between baseline PA and subsequent depression. They also found evidence that even
low levels of PA can have preventative effects on depression, which supported the findings of previous research (e.g., Teychenne, Ball, & Salmon, 2008). Many of these prospective studies used high quality methodology and provided evidence of the causal relationship between PA and subsequent decreases in depression (Mammen & Faulkner, 2013).

One proposed mechanism for this causal link is through the anti-inflammatory effect of regular PA on the neuroimmune system (Eyre & Baune, 2012; Peterson, Charlson, Wells, & Altemus, 2014). This mechanism is outlined by the cytokine model of depression, which proposes that proinflammatory biomarkers from the neuroimmune system are involved in the development of depression symptoms in both pre-clinical and clinical populations (Dantzer, O’Connor, Freund, Johnson, & Kelley, 2008; McAfoose & Baune, 2009). Specifically, the production of inflammatory biomarkers (e.g., CRP, TNF-α, IL-6, and IL-1β) and immune disregulation can affect neural circuitry by influencing neurotransmitter metabolism, neuroendocrine function, synaptic plasticity and growth factor production (Loftis, Huckans, & Morasco, 2010). These changes on neuroimmune pathways can lead to depression-like symptoms (Dantzer, O’Connor, et al., 2008; Eyre et al., 2013; Howren et al., 2009). In addition, the presence of chronic stress may play a role in depressive because stress precedes a majority of clinical depressive episodes (Bartolomucci & Leopardi, 2009; Möller-Leimkühler, 2010). While the quality of studies measuring chronic stress have widely varied (Eyre & Boyne, 2011), stress can result in similar proinflammatory responses like depression (Kop et al., 2008). Specifically, IL-6, CRP, and TNF-α can be elevated in response to chronic stress (Amati et al., 2010; Kop et al., 2008).
PA has a similar neuroimmune response for individuals experiencing stress or
depression due to decreases in CRP, IL-6, IL-1β, and TNF-α (Albert et al., 2004; Eyre &
Baune, 2012; Glynn et al., 2007; Hamer et al., 2012; McMurray & Andersen, 2010). This
is possibly due to decreases in proinflammatory visceral fat mass and the anti-
-inflammatory environment that is created after PA. Hamer and colleagues (2012)
collected data on PA, CRP, and IL-6 for 4289 men and women over a 10-year period.
Participants who met the PA recommendations for 150 minutes of moderate and
vigorous activity at baseline had lower CRP and IL-6 concentrations than those who did
not achieve 150 minutes of activity per week. The results also indicated that maintaining
regular PA over the course of the study was associated with lower proinflammatory
biomarkers. However, PA can have anti-inflammatory effects independent of changes in
body fat so additional research is still needed in this area (Glynn et al., 2007).

PA not only plays a role in improving depression symptoms, but it also can have
beneficial effects with other co-morbidities. Higher levels of moderate and vigorous PA
can prevent and decrease symptoms related to both CVD and metabolic syndrome
(McMurray & Andersen, 2010; Thompson et al., 2003). For example, PA is associated
with decreases in triglycerides, coronary artery calcium and an increase in high-density
lipoprotein (Ahmed, Blaha, Nasir, Rivera, & Blumenthal, 2012). In addition, Sattelmair
and colleagues (Sattelmair et al., 2011) conducted a meta-analysis of 33 prospective
cohort studies that investigated the dose-repose relation between PA and CVD.
Specifically, the authors investigated whether greater amounts of PA were related to
lower CVD risk. They reported that healthy individuals achieving at least 150 or 300
minutes of PA per week had a 14% and 20% lower risk for CVD compared to those who
did not meet the guidelines, respectively. Previous research has also found that PA can reduce inflammation in patients with CVD, especially CRP (Eyre & Baune, 2012; Peterson et al., 2014). Swardfager and colleagues (2012) evaluated 23 exercise interventions that included participants with CVD. Proinflammatory biomarkers were measured before and after aerobic exercise interventions, and each intervention lasted at least two weeks. CVD was diagnosed using a medical history form. The authors reported that CRP and IL-6 concentrations were lower after the exercise intervention with CRP exhibiting one of the greatest reductions.

The role of low-grade, systematic inflammation in both depression and CVD provides a mechanism to explain how PA can improve both diseases. For example, Whooley and colleagues (2014) followed 1000 participants over a 5-year period to investigate the association between depression and CVD. They reported that those with depression symptoms were less likely to be physically active and had a higher mean body mass index and CRP concentrations. In addition, participants with depression symptoms had a 31% higher rate of cardiovascular events, and physically inactivity was associated with 44% higher rate of cardiovascular events. These participants also had more cardiovascular events (e.g., myocardial infarction, heart failure, and diabetes), but the relationship between depression and CVD decreased by 31.7% after adjusting for PA.

In regards to the anti-inflammatory effects of exercise, Gleeson and colleagues (2011) discussed several possible mediators for this effect. For example, decreases in visceral fat from PA is associated with a decrease in the release of proinflammatory biomarkers (e.g., IL-6 and TNF-\(\alpha\)). As a result, the decrease in proinflammatory
biomarkers is related to lower amounts of stored body fat. However, this is evidence that the anti-inflammatory effects of PA can occur without the loss of body fat (Glynn et al., 2007; Ross & Bradshaw, 2009). Other possible mediators include the various changes that occur in the body to create an anti-inflammatory environment. While IL-6 is considered to be an inflammatory biomarker, it does play a role in decreasing inflammation due to PA (Gleeson et al., 2011). After PA, the active skeletal muscles result in a sharp increase in IL-6, which suppresses TNF-α and IL-1β and increases anti-inflammatory cytokines, such as IL-1RA, IL-10, and also cortisol from the HPA axis. Other possible mediators may also exist, including reduced expression of Toll-like receptors on monocytes and macrophages, inhibition of adipose tissue infiltration, and an increase in the circulating numbers of T_{Reg} cells (Gleeson et al., 2011).

Role of Physical Fitness with Depression and CVD

Many studies have investigated the effect of PA on inflammation (Glynn, McFarlin, & Markofsky, 2007), but more information is still needed regarding the role of physical fitness (Buchan, 2012). PA and physical fitness are regularly used interchangeably, but they represent two different concepts. PA is a behavior that describes what a person does, whereas physical fitness is a biological trait or characteristic (Plowman & Meredith, 2013). Specifically, physical fitness is defined as “a set of attributes that people have or achieve that relates to the ability to perform physical activity” (Caspersen et al., 1985). It can be improved as a result of a person being physically active or exercising and reflects a person’s ability to perform specific physical tasks (Institute of Medicine, 2013). These tasks have historically reflected skills related to athletic performance (e.g., agility, balance, power, reactivity, and speed). Starting in
1978, a transition began with the South Carolina Fitness Test to focus on aspects of health-related fitness (HRF), which includes cardiorespiratory endurance (or aerobic capacity), body composition, muscular strength and endurance, and flexibility (Jackson, 2006).

In regards to the relationship between HRF and depression, Becofsky and colleagues (Becofsky et al., 2015) analyzed data from 12,599 participants in the Aerobics Center Longitudinal Study who participated in the study between 1979 and 1998. Specifically, they investigated the relationship between depression and physical fitness (i.e., cardiorespiratory endurance) with three different measure of body composition (i.e., BMI, body fat percentage, and waist-to-hip ratio). The authors found that low cardiorespiratory endurance was a stronger indicator of the onset of depression than any of the three measures of fatness. Therefore, Becofsky et al. (2015) recommended that people should be encouraged to improve their cardiorespiratory endurance regardless of current body fatness. These results were supported by previous research with other adults (e.g., Dishman et al., 2012) and also adolescents. Rieck and colleagues (2013) found that adolescents who were not classified as being in the Healthy Fitness Zone for cardiorespiratory fitness had significantly higher odds of elevated depression (odds ratio = 1.71, 95% CI = [1.03, 2.84]). Participants’ body composition was not a statistically significant predictor of depression. However, both Becofsky et al. (2015) and Rieck et al. (2013) used a self-report measure for depression so additional information is needed regarding the relationship between biomarkers and HRF with emerging adults.
To investigate the relationship between HRF with depression and inflammation, Casey (2013) conducted a study with 96 participants who were enrolled in phase-II cardiac rehabilitation. She found evidence that physical fitness (i.e., exercise capacity or the time that maximum heart rate was reached in metabolic equivalents) moderated the relationship between depression and IL-6. Specifically, a positive relationship between depression and IL-6 was found for those with lower levels of physical fitness. Depression was also negatively related to other factors, such as obesity, higher levels of body mass index, and age. Thus, improving HRF may be another beneficial alternative for those who do not wish to use medication or have not responded strongly to drug therapy (Casey, 2013).

Compared to depression, the relationship between HRF and CVD has been more widely studied. There is consistent evidence that low levels of HRF (e.g., poor cardiorespiratory endurance and high body fat percentage) corresponds with a greater risk of cardiovascular disease (e.g., Carnethon et al., 2003; Countryman et al., 2013; Dishman et al., 2012; Gerber, Lindwall, Lindegård, Börjesson, & Jonsdottir, 2013; Laaksonen et al., 2002). In regards to the benefits of improving different aspects of HRF on health outcomes, a large focus has been placed on the importance of either cardiorespiratory fitness or body fat percentage. For example, Lee, Jackson, and Blair (1998) analyzed data from 21,925 men over an eight-year period from the Aerobic Center Longitudinal Study. Each participant completed a maximal treadmill exercise test and a body composition assessment as part of a complete preventative medicine examination. After adjusting for age, examination year, cigarette smoking and alcohol intake, the authors reported that the relative risk for all-cause mortality was lower in fat
but fit men compared those who were lean but unfit. This provided initial evidence that
the negative health consequences of excess adiposity might be reversed by improving
cardiorespiratory fitness.

In addition, Janssen and Cramp (2007) conducted a cross-sectional study with a
national representative sample of 1,561 adolescents from the National Health and
Nutrition Examination Survey 1999-2002. The purpose of their study was to examine
the relation between cardiorespiratory fitness and metabolic syndrome and to determine
whether this relationship was consistent across sex and ethnicity. They found that
higher levels of CRF was associated with lower odd ratios for each aspect of metabolic
syndrome (i.e., high waist circumference, blood pressure, triglycerides, glucose, and low
HDL) across sex and ethnicity. These findings were supported by a study conducted by
Lee and colleagues (2005) who found that higher levels of cardiorespiratory fitness was
associated with lower health risks for metabolic syndrome across different levels of
visceral and subcutaneous fat.

To investigate the long-term effects of fitness, a longitudinal cohort study by
Carnethon and colleagues (Carnethon et al., 2003) followed over 2700 participants for
15 years. The participants completed the Bake protocol on a treadmill at five time
points, and CVD was measured using metabolic syndrome. The authors reported that
the participants in the bottom 20th percentile for fitness were three to six times more
likely to develop diabetes, hypertension, and metabolic syndrome that those in at least
the 60th percentile. Those who improved their fitness level for at least seven years
decreased their risk for diabetes and metabolic syndrome. Previous research has also
indicated that improving cardiorespiratory fitness can be beneficial even in the absence
of weight loss (Hainer et al., 2009). However, other studies have reported that body fat is more important for health outcomes. For example, Christou et al. (2005) found that body fatness (i.e., BMI, percent body fat, and waist circumference) was a better predictor of CVD risk factors than cardiorespiratory fitness in 135 healthy men across a range of metabolic, hemodynamic, and hemostatic risk factors. Thus, it is important to consider that both determinants are interrelated due to the positive relationship between PA and fitness and the negative relationship between PA and fatness (Hainer et al., 2009).

In regards to proinflammatory biomarkers, a number of studies have investigated the effect of PA and exercise interventions (Glynn, McFarlin, & Markofsky, 2007), but more information is still needed regarding the role of HRF (Buchan et al., 2012). The current literature indicates that VO$_{2\text{max}}$ is negatively associated with CRP and IL-6 (Aronson et al., 2004; Kullo et al., 2007; Plaisance & Grandjean, 2006; Thomas & Williams, 2008). For example, a study by Ruiz and colleagues (Ruiz et al., 2007) included 142 children aged 9-10 year-olds, and the authors found that low-grade inflammatory markers were negatively related to cardiorespiratory fitness and positively related to fatness (i.e., skinfold thickness). Furthermore, previous research has indicated that fitness moderates the relationship between PA and inflammation. Franks and colleagues (2004) studied 874 healthy participants in a cohort study to investigate the relation between PA and metabolic syndrome and to determine whether fitness moderated this relationship. They measured PA with individually calibrated heart rate against energy expenditure, and VO$_{2\text{max}}$ was predicted from a submaximal exercise stress test. Impedance biometry was used to estimate fat and fat-free mass. The results
indicated that participants in the lowest fitness group benefitted the most from being physically active due to decreases in inflammation. As a result, it might be beneficial to consider a person’s current PA behaviors and HRF when assessing biomarkers for depression and CVD. However, while the current literature regarding HRF has predominately focused on cardiorespiratory endurance or body composition, there is still a need for information regarding the role of other aspects of HRF (e.g., muscular strength and endurance; Buchan et al., 2012). Thus, utilizing several components of HRF might be helpful to evaluate health status because physical fitness is an integrated measure that incorporates many bodily system (e.g., skeletomuscular and cardiorespiratory; Artero et al., 2011; Ortega et al., 2008).

Conclusion

Depression and CVD are two important health issues that can develop during young adulthood. In fact, both of these diseases are projected to be the top two causes of years lost due to ill-health, disability, or early death for all ages by 2020 (Reddy, 2010). In order to address these health issues, establishing effective and efficient methods to measure the severity of depression and CVD at an earlier age may help prevent or reduce the personal, social, and economic burden associated with these diseases (Buchan et al., 2011). Because low-grade and chronic inflammation is associated with the development of both depression and CVD, regular PA and improving HRF might be beneficial due to their anti-inflammatory effects. For example, regular PA, higher cardiorespiratory fitness, and lower body fat has been associated with lower concentrations of proinflammatory biomarkers (e.g., CRP, IL-6, IL-1β, and TNF-α), fewer depression symptoms, lower stress, and a healthy CVD profile. However,
less information is available regarding the role of other aspects of HRF (e.g., muscular strength and endurance), and more information is needed about whether HRF moderates the relationship between PA and these health outcomes.


Institute of Medicine. (2012). *Fitness measures and health outcomes in youth*. Washington, D.C.


