



# Endothelin-1 and Exercise Intensity in Sedentary Adolescents with Obesity

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## Abstract

Inactivity combined with obesity during adolescence increases the risk of future cardiovascular disease. The study purpose was to compare the influence of differing intensities of exercise on endothelial function in sedentary adolescents with obesity. Participants were randomized to one of two groups in a 6-week exercise intervention: moderate intensity (MOD) or high intensity interval exercise (HIIE). Endothelial function was assessed pre- and post-intervention via fasted serum levels of endothelin-1 (ET-1). Pre-measures of ET-1 concentrations were elevated at baseline. No significant differences in ET-1 were found between or within exercise groups. However, in the HIIE group, ET-1 was inversely associated with percentages of age predicted maximal heart rate achieved during the intervention ( $p=0.035$ ,  $r=-0.567$ ). The exercise interventions did not positively change ET-1 levels, yet participants who exercised at higher intensities in the HIIE group experienced greater decreases in ET-1.

**Keywords:** childhood obesity, endothelial function, high intensity interval exercise

## 1. Introduction

The prevalence of obesity in adolescents has become a major public health concern in the United States. Currently, the highest prevalence rate of obesity among individuals under 20 years of age is found in adolescents aged 12 – 19 (18.4%) (Ogden, Carroll, Kit, & Flegal, 2012). These statistics highlight an association between obesity and low-grade, chronic inflammation, predisposing adolescents to cardiovascular and metabolic abnormalities, and setting the stage for advanced cardiovascular disease (CVD) in adulthood (Daniels, 2006; Giordano et al., 2011; Reinehr, Kiess, de Sousa, Stoffel-Wagner, & Wunsch, 2006). Increased sedentary behavior may be a substantial contributor for the increasing rates of obesity among adolescents over the last 50 years (Davison, Marshall, & Birch, 2006; Gortmaker et al., 1996; Rey-Lopez, Vicente-Rodríguez, Biosca, & Moreno, 2008). Some studies have reported adolescents spending approximately 45% of their leisure time in sedentary activities (Hardy, Bass, & Booth, 2007). Furthermore, these behaviors increased by 28% in adolescent girls during a 2.5 year period, from 2000 to 2002, demonstrating a trend of

increased adverse health risks (Hardy et al., 2007). Sedentary behavior, similar to obesity, is also independently associated with comorbidities in adolescence and is believed to set the stage for a host of diseases in adulthood or earlier. Specific popular sedentary activities such as viewing television and playing video games, have been linked to low cardiorespiratory fitness in girls (Martinez-Gomez et al., 2011), high cardiometabolic risk scores (Pahkala et al., 2012; Rey-López et al., 2013), and elevated markers of endothelial dysfunction (Martinez-Gomez et al., 2012) and blood pressure (Gopinath et al., 2011).

The cumulative effect of obesity and sedentary behavior may be responsible for a greater number of deleterious health outcomes, expediting the onset of CVD. Both obesity and physical inactivity are often accompanied by elevated pro-inflammatory and reduced anti-inflammatory markers, which are risk factors for CVD (Cao et al., 2009). Furthermore, if obesity and prolonged sedentary behavior occur during childhood and adolescence, the combination of the two may contribute to arterial abnormalities at a young age. Endothelial dysfunction is a pathological state of the endothelium and is one of the first signs of atherosclerosis and subsequent CVD. The process of atherosclerosis and the development of fibrous plaque lesions have been identified in the arteries of children as young as two years old (Berenson et al., 1998). Furthermore, adolescents with obesity have demonstrated greater endothelial dysfunction compared with their lean counterparts (Duck & Hoffman, 2007). However, the cumulative effects of sedentary behavior and obesity on endothelial function have not yet been assessed in youth.

Endothelial function can be assessed and measured via multiple methods. Monitoring serum levels of endothelin-1 (ET-1) is a non-invasive technique for identifying changes in endothelial function. Due to the multitude of factors affecting the clearance of serum ET-1 concentrations, assessing ET-1 in vascular smooth muscle cell may be more telling of the changes to endothelial function. However, overall serum concentrations may be a useful marker of endothelial function. ET-1 is a potent vasoconstrictor and functions as a pro-atherosclerotic protein contributing to platelet activation, lipid oxidation, and growth and proliferation of vascular smooth muscle cells. Expressed by endothelial cells, levels of ET-1 are known to be elevated with aging, obesity, type 2 diabetes mellitus (T2DM), and hypertension. Elevated ET-1 results in alterations in the vascular bed of smooth muscle and contributes to the pathology of vascular disorders including endothelial dysfunction (Mather, Mirzamohammadi, Lteif, Steinberg, & Baron, 2002; Nyberg, Mortensen, & Hellsten, 2012; Van Guilder, Westby, Greiner, Stauffer, & DeSouza, 2007). In children and adolescents, elevated levels of ET-1 have been found in those with obesity, hypertension, and T2DM, indicating potential danger for CVD (Głowińska et al., 2004).

Exercise and habitual participation in physical activity have been found to decrease plasma concentrations of ET-1 in adults, while similar outcomes in adolescents have yet to be identified (Nyberg et al., 2012; Van Guilder et al., 2007). With the dangers of obesity many adolescents now face, determining effective frequency, intensity, and duration of exercise recommendations has become vital. Very vigorous PA, defined as activity ranging from 80-95% of maximal heart rate, is often referred to as high intensity interval training (HIT) or high intensity interval exercise (HIIE) (Bartlett et al., 2011; Tjonna et al., 2009; Warburton et al., 2005; Wisloff et al., 2007). Training studies utilizing HIIE have been conducted in both adults and children in order to determine the effects on cardiovascular changes and inflammation when compared with moderate exercise. While both moderate and vigorous PA can produce significant cardiovascular benefits, the improvements appear to be greater with higher intensity activities (Gutin et al., 2002; Starkoff, Eneli, Bonny, Hoffman, & Devor, 2014). Adaptations to HIIE often include increased nitric oxide (NO) bioavailability as a result of increased shear stress. One study indicated that following three months of HIIE in adolescents with obesity led to a significant increase in NO bioavailability, reduction in fasting blood glucose, and increase in adiponectin compared with the moderate exercise group, and a subsequent improvement in endothelial function (Tjonna et al., 2009).

There is a dearth of literature on the impact of HIIE on endothelial function as measured via plasma ET-1 in adolescents with obesity, specifically sedentary adolescents with obesity. Our purpose was to compare the effects of exercise of differing intensities (HIIE vs. MOD) on endothelial function, as measured by a marker of endothelial function, plasma ET-1, in sedentary adolescents with obesity. Our hypothesis was that HIIE would result in greater improvements in endothelial function via decreases in ET-1 as compared to moderate intensity exercise.

## 2. Methods

### 2.1 Participants

Otherwise healthy, sedentary, adolescents with obesity were recruited into the Children Active to Stay Healthy (CASH) study from clinics at Nationwide Children's Hospital (NCH) in Columbus, OH. Obesity was defined as BMI  $\geq$  95<sup>th</sup> percentile for age and sex as defined by the Centers for Disease Control (CDC) (Kuczmarski et al., 2002). Participants were excluded from the study if they reported an acute inflammatory disease or febrile illness, recent trauma or injury, asthma requiring steroid use or hospitalization within the prior 3 months, inflammatory/immune disorders (e.g. lupus), and any renal, cardiac, or liver disease. All participants self-identified as sedentary defined by  $\leq$  30 minutes of MVPA on 5 or more days per week. Information about participants was collected via parental report during the initial intake phone call.

Thirty-four participants were randomized to MOD (n=16; 6 males and 10 females) or HIIE (n=18; 8 males and 10 females) via a random number generator. All participants and legal guardians provided written informed assent and consent, respectively. The study protocol was approved by the Institutional Review Boards of the participating institutions and conducted in accordance with the Helsinki Declaration of 1975. The study trial was registered at

ClinicalTrials.gov (<http://clinicaltrials.gov>) under the trial number NCT01821313. Closure of the intervention was defined by completion of 75% of the exercise sessions (14 of 18) and all follow-up testing including fitness and laboratory assessments. Participants that were unable to meet the completion criteria were excluded from data analysis (n=1).

## 2.2 Experimental Design

The study was a randomized pretest/posttest experimental design conducted at NCH and The Ohio State University (OSU) in Columbus, Ohio.

## 2.3 Study Measures

All study measures were obtained prior to randomization at baseline, and within one week following completion of the 6-week exercise intervention.

### 2.3.1 Anthropometric Measurements

Height and body mass were measured in minimal clothing to the nearest 0.5 cm and 0.1 kg, with a stadiometer and traditional scale, respectively. BMI was calculated as weight (kg)/height (m<sup>2</sup>). Waist and hip circumference were measured to the nearest 0.5 cm using standard anthropometric tape. Waist circumference was measured midway between the lowest rib and iliac crest and hip circumference at the point of greatest protrusion (Wang, Thornton, Kolesnik, & Pierson, 2000). Body fat percentage was measured via Bod Pod air-displacement plethysmography (Life Measurements Instruments, Concord, CA). Prior to body fat percentage measurement, the Bod Pod was calibrated for volume and mass. Participants entered the Bod Pod in a fasted state, wearing minimal, tight fitting clothing and a swim cap. Density models were used based on age and sex (Lohman, 1989).

### 2.3.2 Laboratory Assessment

Prior to participation in and within one week of completion of the exercise intervention, participants reported to Clinical Research Services at NCH in the morning for a fasted venous blood draw. The blood draw was performed after a 12-hour overnight fast, to obtain ET-1, and subsequently assayed a single time via serum collection using a 1-25 Radiogamma counter (Inter Science Institute, Inglewood, CA).

## 2.4 Intervention

Participants were randomized to receive either MOD or HIIE training as stated previously. For both groups, activity sessions were performed on a cycle ergometer (Lode, The Netherlands) and completed on three non-consecutive days per week over a 6-week period, for a total of 18 training sessions. Participants began every training session with a five-minute warm-up at 50-55% of age predicted maximal heart rate (APMHR) as determined by the following equation:  $APMHR = 220 - \text{age}$  (Fox & Haskell, 1968). Heart rates were measured via Polar heart rate monitors (Polar Electro Inc, Lake Success, NY). Participants were reminded of personal HR ranges and instructed to stay within the range during the entire session (MOD), or during the two-minute interval bouts (HIIE).

Following the warm-up, the MOD group cycled continuously for 30 minutes at 65-70% of APMHR. Participants in the MOD group were permitted to cycle at any speed and workload as long as they stayed within the specified target HR range. The HIIE group performed 10, two-minute cycling intervals at 90-95% of APMHR, with one minute of active recovery at 55% of APMHR between each interval for a total of 30 minutes. Participants in the HIIE group were instructed to cycle at an "all-out" pace, while the workload was adjusted by the study staff in order to maintain target HR range. Both MOD and HIIE ended with a 5-minute cool-down at 50-55% of APMHR. HR was measured every two minutes for both MOD and HIIE groups. This protocol was designed based on previous research (Babraj et al., 2009; Little et al., 2011; Warburton et al., 2005) and modified to ensure this population would be able to maintain the pre-determined duration and intensity with limited risk of injury.

## 2.5 Statistical Analyses

Descriptive statistics (means, medians, percentiles, ranges) were calculated and provided for all outcome variables and demographics. The primary outcome variable was difference in ET-1 concentration changes between MOD and HIIE groups. The secondary outcome was change in ET-1 serum concentration in both groups, post-6-week exercise intervention. Paired *t* tests were performed to compare pre- and post-intervention mean levels of ET-1 within groups. Initial comparisons of measures between the two intervention groups were assessed using *t* tests. In final modeling, a two-way ANOVA with repeated measures was performed to test the differences between participants in the MOD and HIIE groups. The initial analysis we conducted revealed non-significant results (both the *t*-tests and the ANOVA) and to further explore the magnitude of change, we performed secondary analyses to explore the effect sizes (Cohen's *d*). An effect size of 0.25 was identified between exercise groups, highlighting a small difference in the magnitude of treatment. All analyses were conducted using IBM SPSS Statistics 20.0 (IBM Corp, Armonk, NY).

## 3. Results

### 3.1 Baseline Characteristics

At baseline, *t*-tests revealed that the two groups demonstrated no significant differences in height, weight, body mass index (BMI), BMI z score (BMIZ), body fat percentage (BF%), and waist-to-hip-ratio (WHR) (Table 1).

Table 1. Subject characteristics

	<b>Total Sample (n = 27)</b>	<b>MOD (n = 13)</b>	<b>HIIE (n = 14)</b>
Age (years)	14.7 ± 1.5	14.5 ± 1.4	14.9 ± 1.6
Height (cm)	167.2 ± 9.4	166.8 ± 9.9	167.4 ± 9.3
Weight (kg)	105.4 ± 20.7	108.3 ± 23.2	102.7 ± 18.5
BMI (kg/m <sup>2</sup> )	37.6 ± 6.0	38.7 ± 6.7	36.5 ± 5.4
BMIz	2.38 ± 0.35	2.42 ± 0.37	2.34 ± 0.34
Body fat (%)	43.8 ± 7.1	44.3 ± 8.1	43.4 ± 6.2
WHR	0.85 ± 0.06	0.87 ± 0.06	0.84 ± 0.05

BMI= body mass index; BMIz= body mass index z-score; WHR= waist-to-hip ratio;  $VO_{2max}$ = maximal oxygen consumption. All data are presented as mean ± SD.

In total, 27 of the 34 participants completed 87.3 ± 7.7% of the scheduled exercise sessions (Figure 1).

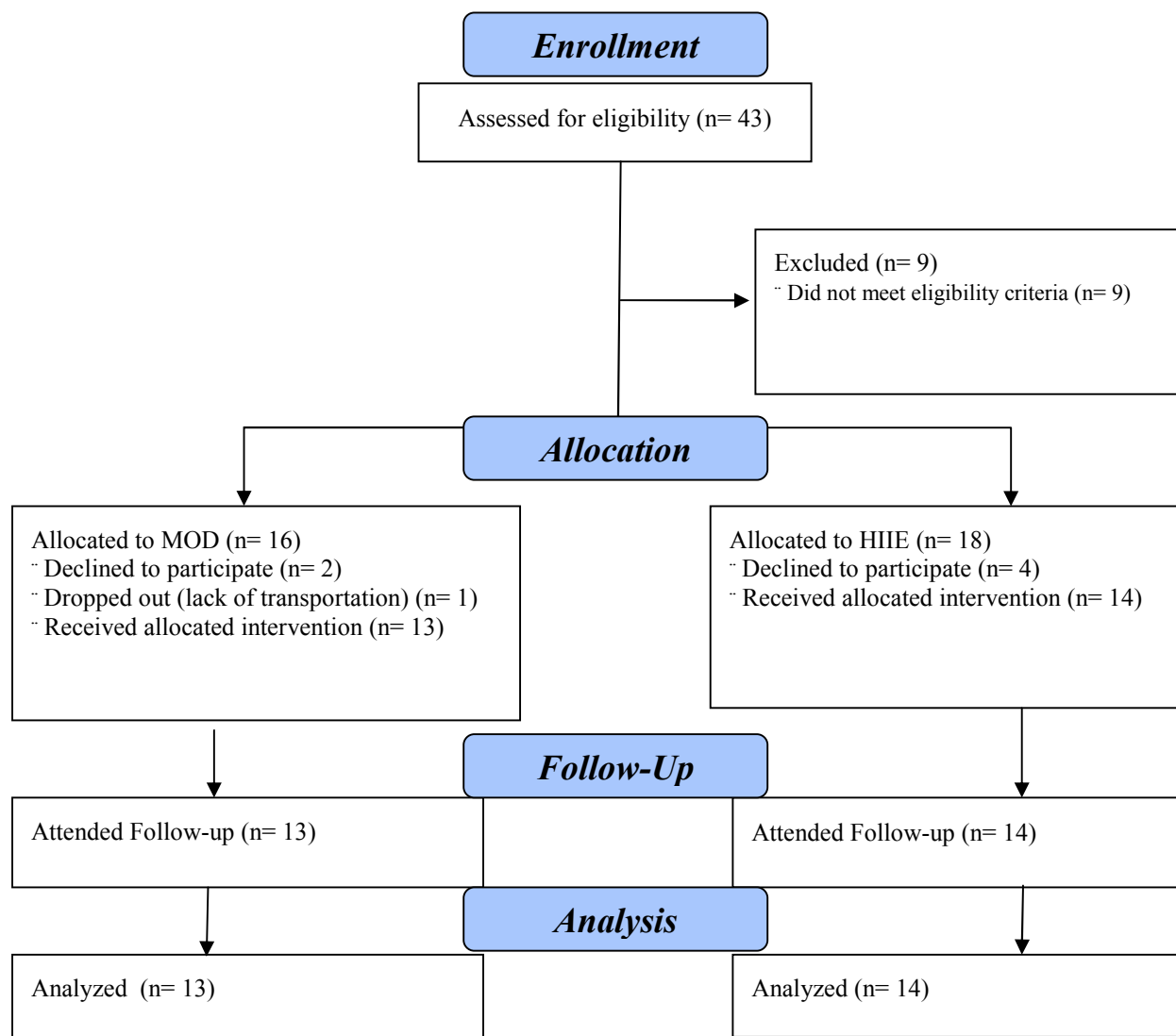


Figure 1. Children Active to Stay Healthy (CASH) consort diagram

Participants in the MOD group maintained 65-70% of APMHR during 89.5 ± 14.4% of the attended sessions, while the HIIE participants stayed in the prescribed heart rate zone (90- 95% of APMHR) for 50.9 ± 40.7% of attended sessions. The HIIE group attained an average heart rate of 88.8 ± 4.1% of age predicted maximum heart rate (APMHR) during exercise. There were no significant changes in weight or BF% between or within groups following the intervention (Table 2).

### 3.2 Endothelin-1

Mean baseline ET-1 was 4.1 ± 2.5 pg/mL and mean post-intervention ET-1 was 4.2 ± 2.5 pg/mL. Paired sample t-tests revealed no significant differences in ET-1 change from pre- to post-intervention.

No statistical differences were detected in ET-1 values between HIIE and MOD groups at baseline or following the exercise intervention. ET-1 decreased slightly and non-significantly in the HIIE group and increased slightly in the MOD group (Table 2).

Table 2. Changes in body composition and endothelin-1 from pre- to post-intervention

	Total (n = 27)	MOD (n = 13)	HIIE (n = 14)
Weight (kg)	0.82 ± 2.57	1.45 ± 3.23	0.24 ± 1.58
BF (%)	-0.47 ± 1.95	-0.22 ± 2.08	-0.71 ± 1.87
WC (cm)	-1.39 ± 4.61	-0.62 ± 3.90	-2.11 ± 5.24
WHR	-0.02 ± 0.03*	-0.01 ± 0.04	-0.02 ± 0.03
BMI (kg/m <sup>2</sup> )	0.16 ± 0.85	0.19 ± 1.08	0.14 ± 0.60
BMIz	-0.001 ± 0.057	-0.002 ± 0.069	0.000 ± 0.047
ET-1 (pg/mL)	0.10 ± 3.21	1.01 ± 3.72	-0.70 ± 2.88

MOD = Moderate intensity; HIIE = High intensity interval exercise; BF% = body fat percent; WC = waist circumference; WHR = waist-to-hip ratio; BMI = Body mass index; BMIz = BMI z score; ET-1 = endothelin-1; All data is presented as means ± SD; \*significant change from pre- to post-intervention,  $p = 0.020$ .

Pearson correlation showed that, in the HIIE group, the change in ET-1 was significantly and negatively associated with percent of APMHR achieved during the intervention ( $p = 0.035$ ;  $r = -0.567$ ), such that higher intensity achieved during HIIE was associated with greater reductions in ET-1 (Figure 2).

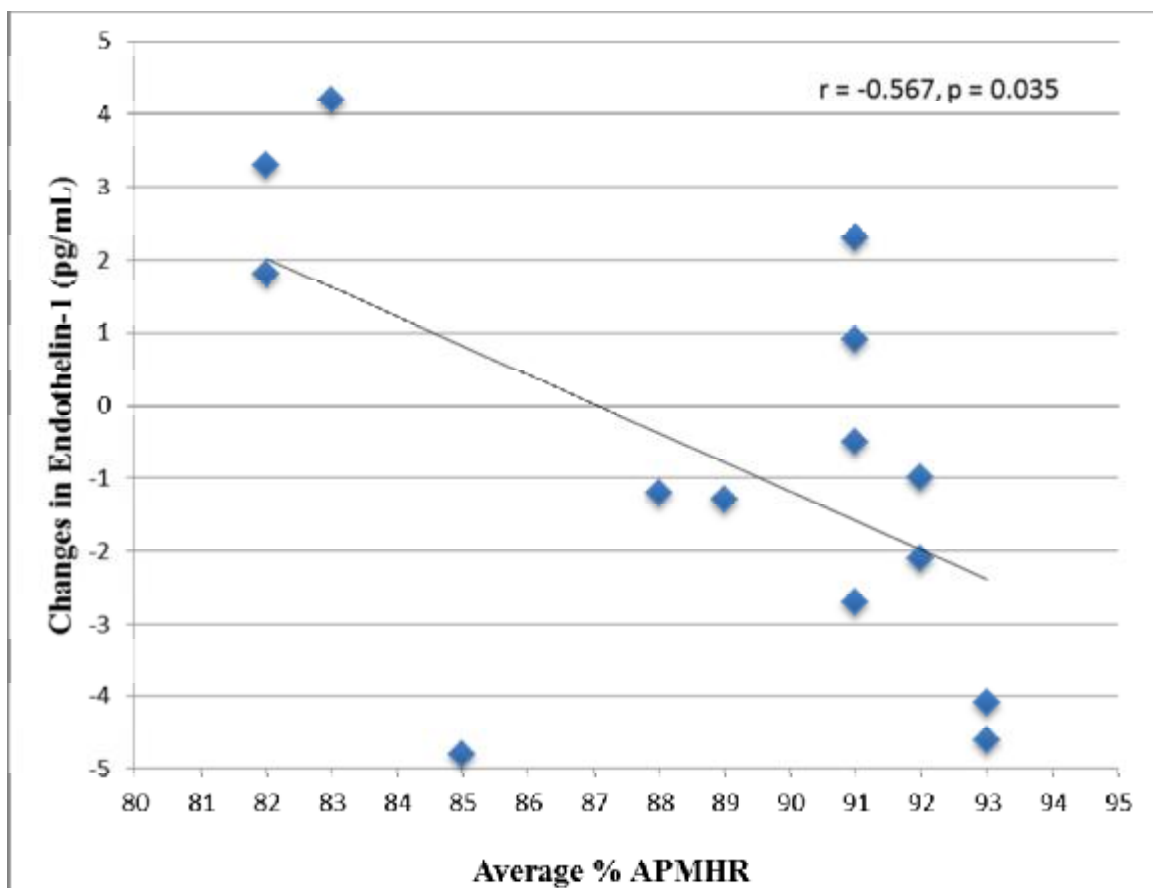


Figure 2. Relationship of change in endothelin-1 and average exercise intensity in high intensity interval exercise group

#### 4. Discussion

High intensity exercise interventions have been found to elicit changes in endothelial function, often more substantially than moderate or lower intensity activities (Tjonna, Rognmo, Bye, Stolen, & Wisloff, 2011; Warburton et al., 2005). Yet, in the current study, no statistical change in endothelial function, as measured by ET-1 serum concentration, was identified between or within the exercise groups. Neither MOD nor HIIE produced significant changes in ET-1, nor did the exercise intensities differ in their overall effects on ET-1. This may be due to the inability of all participants in the HIIE group to maintain the prescribed exercise intensity. However, importantly, participants in the HIIE group who

achieved higher intensities of exercise during the intervention had greater decreases in ET-1 serum concentrations and subsequent positive change. Similarly, Maeda et al. (2001) identified improvements to ET-1 in adults engaging in exercise intensities at 70% of aerobic capacity, a much lower intensity than what was used with our participants (Maeda et al., 2001).

Our participants demonstrated substantially elevated resting ET-1 serum concentration compared to normal values (0.1 - 3.0 pg/mL) or other adolescents with obesity (0.96 pg/mL) (Głowińska et al., 2004). However, it should be noted that serum concentrations of ET-1 may be a result of factors influencing rates of clearance. Still, in conjunction with the effects of obesity on endothelial function, sedentary behaviors may further exacerbate endothelial dysfunction. Nosova et al. (2014) found that after five days of bed rest, healthy individuals demonstrated decreased endothelial function measured via flow mediated dilation (Nosova et al., 2014). It is believed that physical inactivity promotes the production of vascular reactive oxygen species, a significant contributor to endothelial dysfunction (Laufs et al., 2005). Ultimately, the combination of obesity and chronic sedentary behavior, as exemplified by our participants, may contribute to a greater magnitude of endothelial dysfunction than just one of the two.

Research has consistently and clearly identified exercise as an appropriate tool to improve cardiovascular function in children and adolescents, yet it remains unclear what intensity may elicit the greatest changes (Watts, Beye, Siafarikas, Davis, et al., 2004; Watts, Beye, Siafarikas, O'Driscoll, et al., 2004; Woo et al., 2004). Increased shear stress as a result of greater blood flow during exercise contributes to the release of NO in the vascular endothelium. Further, the protective effects of exercise appear to be intensity related (Green, Maiorana, O'Driscoll, & Taylor, 2004; Tjonna et al., 2009; Warburton et al., 2005). Higher exercise intensities result in substantially greater blood flow through the vasculature and improved shear stress mediated upregulation of NO-synthase, the enzyme responsible for producing NO (Green et al., 2004). The increased NO bioavailability thus allows for more efficient vasodilation and improved blood flow (Kelly et al., 2004). Studies have identified an inverse relationship between NO and ET-1 in the vascular endothelium in which the NO production pathway inhibits the production of ET-1 (Boulanger & Lüscher, 1990). Therefore, higher intensities of exercise may elicit greater NO bioavailability, thus contributing to reduced ET-1.

Very few studies have compared the effects of HIIE and moderate exercise in children and adolescents with obesity. While HIIE may seem extreme, especially for an obese and sedentary participant, it has been shown to be attainable by this population and has been found to elicit substantial improvements to cardiovascular health. Tjonna et al. (2009), for example, found that three months of HIIE in obese adolescents led to significant improvements in NO bioavailability compared to those receiving moderate exercise. Following three months of exercise consisting of four, 4-minute intervals at 90% of maximal heart rate, separated by 3 minutes at 70% of maximal heart rate, the HIIE group also demonstrated reduced fasting blood glucose and increased levels of adiponectin (Tjonna et al., 2009). While our participants displayed no significant changes in endothelial function, as measured by serum ET-1 concentrations, following either HIIE or MOD intensity of exercise, we did identify that those engaging in HIIE who achieved higher percentages of APMHR demonstrated greater decreases in ET-1. To the best of our knowledge, this study is the first to show that higher intensity exercise may result in greater reductions in ET-1, independent of changes in body composition.

Limitations to the current study include lack of nutrition and behavior modification and short duration of the exercise intervention (6 weeks). This duration was previously identified as a sufficient amount of time to elicit changes in endothelial function (Woo et al., 2004). It is therefore plausible that a similar protocol accompanied by nutrition and behavioral components, carried out over a longer period of time would have found significant reductions in ET-1. The lack of adherence to the prescribed exercise protocol for some participants in the HIIE may also have impacted the results of this study. Although we had individual study staff encouraging each participant, inability to maintain prescribed intensity may have been a result of lack of motivation. Had all HIIE participants maintained an APMHR of 90-95% for the majority of the sessions, we may have seen greater changes to ET-1.

Current literature has recently found that the equation  $220 - \text{age}$  may overestimate predicted maximal heart rate and, is therefore, not appropriate for estimating maximal heart rate in adolescents (Mahon, Marjerrison, Lee, Woodruff, & Hanna, 2010). Therefore, future research should identify actual maximal heart rates using maximal exercise testing to create an appropriate exercise prescription. Lastly, the current study utilized cycle ergometry as the sole form of exercise during the intervention. Compared to weight-bearing exercises like running or walking, non-weight-bearing exercises rely on less muscle mass and result in a reduced workload, ultimately eliciting a lower heart rate response. Weight-bearing exercises are suggested for future research to elicit higher exercise HR.

In conclusion, we report that sedentary, adolescents with obesity exhibited elevated mean ET-1 values. The exercise intervention did not significantly improve the ET-1 levels, yet those who exercised at higher intensities in the HIIE group experienced a greater decrease in ET-1. By decreasing chronically elevated levels of ET-1 present in obesity, habitual PA may oppose the vasoconstriction associated with obesity, independent of changes in body composition.

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