High-intensity interval training without weight loss improves exercise, but not basal or insulin-induced, metabolism in overweight/obese African-American women

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Running Head: High-intensity interval training and substrate utilization
Abstract

The purpose of this randomized controlled clinical trial was to determine the effect of a 14-week high-intensity interval-training (HIIT) intervention with weight stability on metabolic flexibility, insulin sensitivity and cardiorespiratory fitness in sedentary, premenopausal, non-diabetic, overweight/obese African-American women. Twenty-eight subjects were allocated to one of two groups: HIIT, which performed three sessions/week of four high-intensity cycling intervals; or CON, which maintained their normal level of physical activity. Diet was controlled for all subjects to ensure weight stability. Pre and post intervention, subjects completed an incremental cycling test to limit of tolerance and, following a 10-day high-fat controlled feeding period, a euglycemic-hyperinsulinemic clamp to determine insulin sensitivity and substrate oxidation. Nine members of HIIT (age, 29 ± 4 yr; body mass, 90.1 ± 13.8 kg) and 11 members of CON (age, 30 ± 7 yr; body mass, 85.5 ± 10.7 kg) completed the study. HIIT experienced increased limit of tolerance (post, 1124 ± 202 s; pre, 987 ± 146 s; \( P<0.05 \)), gas exchange threshold (post, 1.29 ± 0.34 L∙min\(^{-1}\); pre, 0.97 ± 0.23 L∙min\(^{-1}\); \( P<0.05 \)) and fat oxidation at the same absolute submaximal work rate compared to CON (\( P<0.05 \) for group-by-time interaction in all cases). However, changes in \( \dot{V}O_{2\text{peak}} \), insulin sensitivity, free-fatty-acid suppression during insulin stimulation and metabolic flexibility were not different in HIIT compared to CON. High-intensity interval training with weight stability increased exercise fat oxidation and tolerance in subjects at risk for diabetic progression, but did not improve insulin sensitivity or fat oxidation in the post-absorptive or insulin-stimulated state.

Key Words: high-intensity interval training; metabolic flexibility; insulin sensitivity; exercise tolerance
Introduction

During fasting and other conditions where blood glucose concentration must be protected, glucose oxidation is reduced and fat oxidation is increased to provide sufficient acetyl-CoA for the tricarboxylic acid cycle (49). Conversely, during post-prandial conditions or when hyperglycemic stimuli are experimentally induced, carbohydrate utilization increases and fat catabolism is suppressed (37). This ability to shift between carbohydrate and fat as fuel (i.e., “metabolic flexibility”) is an important characteristic of healthy function that requires sensitivity to the actions of insulin. Consequently, it is not surprising that metabolic flexibility is reduced when insulin resistance is present with obesity (37). For example, the fasting rate of fat oxidation is lower in skeletal muscle of obese compared to lean subjects (37) and obese subjects also lack the ability to shift to the appropriate fuel after imposition of a eucaloric high-fat diet (59, 62) and during insulin-stimulated conditions (i.e., when rate of fat oxidation should increase and decrease, respectively) (37). There is growing research interest in this “metabolic inflexibility” due to its link to weight gain (65) and the pathogenesis of insulin resistance and type 2 diabetes (37, 62).

Weight loss by dietary and/or surgical intervention increases insulin sensitivity in obese subjects with or without diabetes (25, 27, 34, 37, 47). However, the flexibility required to increase fat catabolism during fasting or when dietary fat intake is increased is not restored by weight loss (2, 37). Furthermore, compared to matched controls, formerly-obese subjects exhibit lower rates of fat oxidation at rest and during recovery from moderate-intensity exercise despite similar rates of fat mobilization (50). Collectively, these findings are consistent with the contention that a mitochondrial defect might be responsible for dysfunctional fat metabolism that is associated with obesity and the pathophysiology of insulin resistance (37, 56).
The chronic performance of endurance exercise (i.e., “endurance training”) increases the activity of mitochondrial enzymes and genes involved in mitochondrial biogenesis (59). These adaptations imply an enhanced ability for muscle mitochondria to oxidize fat and, indeed, for healthy subjects, endurance training allows for a greater reliance on fat oxidation at any absolute submaximal work rate (30, 32). Endurance training also improves insulin sensitivity in untrained healthy young adults (58) and ameliorates age- and disease-related declines in healthy elderly subjects (53) and individuals with impaired glucose tolerance and/or obesity (9, 12, 15), respectively. Furthermore, Goodpaster et al. found that in conjunction with caloric reduction, endurance training increases the fasting rate of fat oxidation in obese subjects with the favorable change being the strongest predictor of improved insulin sensitivity (26). Similarly, endurance training improves fasting fat oxidation in older obese subjects with impaired glucose tolerance (57) and non-obese subjects with type 2 diabetes (61). However, the ability of endurance training to increase fasting fat utilization might depend upon the intensity/volume of exercise, the severity of pathological progression and/or whether caloric restriction and weight loss accompany training (26, 43).

From a traditional standpoint, endurance training involves rhythmic contractions of a significant portion of the body’s large muscle groups at a sustainable percentage of the maximal voluntary contraction (i.e., “aerobic exercise”). However, endurance training has recently been redefined by a “new” protocol comprising relatively short bouts of high-intensity exertion interspersed with periods of low-intensity exercise or rest. This “high-intensity interval training” (HIIT), which has typically been reserved for athletes, has been shown to also be appropriate for untrained individuals due to its time-efficient nature and ability to improve cardiopulmonary fitness; for example, increase the maximal rate of oxygen
consumption (\(\dot{V}O_{2\text{max}}\), the standard index of cardiorespiratory fitness) (4) and lactate threshold (LT, the threshold that demarcates the moderate and heavy exercise intensity domains) (13). There is also a growing body of research which suggests that HIIT is both safe and effective in the clinical setting (28, 41). Interestingly, HIIT-induced cardiorespiratory adaptations appear to be specifically attributable to increased muscle mitochondrial capacity (23, 42); therefore, it is not surprising that HIIT improves insulin sensitivity in normal-weight individuals (3). However, findings regarding the effect of HIIT on insulin sensitivity in overweight/obese subjects have been mixed (14, 24, 31) and the effects of HIIT on metabolic flexibility in overweight/obese subjects has not been investigated.

The purpose of the present randomized controlled clinical trial was to determine the effect of a 14-week HIIT intervention with weight stability on metabolic flexibility, insulin sensitivity and cardiorespiratory fitness in sedentary, premenopausal, non-diabetic, overweight/obese African-American (AA) women. We chose this subject population because AA women have a higher incidence of obesity (39) and metabolic inflexibility (7) and lower cardiorespiratory fitness (e.g., \(\dot{V}O_{2\text{max}}\) and LT; 40, 52), peripheral insulin sensitivity and mitochondrial capacity (17) compared to their white counterparts. AA women are also less physically active with time constraints being the most frequently-cited reason (18). Collectively, these distinctions make this subject population appropriate candidates for an intervention that halts the progression of the diabetic pathophysiology, improves cardiorespiratory fitness and is both time efficient and more enjoyable to perform (5). We hypothesized that compared to control subjects only exposed to pre/post testing, HIIT-trained subjects would exhibit: 1.) improved metabolic flexibility due to increased post-absorptive fat oxidation and insulin-stimulated fat suppression; 2.) improved insulin sensitivity; and 3.) increased \(\dot{V}O_{2\text{peak}}\), gas exchange threshold (GET, a non-invasive measurement that approximates LT) and exercise tolerance.
Methods

Subjects

After initial screening and assessment, 28 healthy, premenopausal (age, 20-40 yrs), sedentary (exercise frequency/duration, <3x/week, 60 min/session), non-diabetic (fasting blood glucose, <110 mg/dL), overweight/obese (BMI, >25 kg/m²) AA women volunteered to participate in this randomized controlled clinical trial. Experimental procedures were submitted to and approved by the St. Luke’s-Roosevelt Institute for Health Science Institutional Review Board and all subjects gave their written informed consent prior to commencement of the study after procedures, associated risks and potential benefits of participation had been explained. Subjects were considered for inclusion only if they self-reported that all four grandparents were AA. Initial screening required subjects to complete a comprehensive medical history and physical activity questionnaire. Exclusion criteria included: 1.) weight change ≥±2 kg within the past three months; 2.) taking any medications that might affect insulin or fat metabolism (including oral contraceptives); 3.) smoking within the past six months; 4.) consuming >2 oz ethanol/day; and/or 5.) having irregular menstrual cycles (e.g., skipping >2 monthly cycles/yr). Subjects who passed this initial screening underwent a full physical examination, which included blood work, resting ECG and oral glucose tolerance test (OGTT) to ensure absence of diabetes (2-h OGTT plasma glucose, <140 mg·dL⁻¹), hyperlipidemia (fasting plasma triglycerides, <350 mg·dL⁻¹ and total cholesterol <300 mg·dL⁻¹) and other chronic illnesses that might affect their capacity to exercise. Eligible subjects were then required to perform a step-incremental cycling test (see below) and ECG was recorded so that subjects displaying an abnormal exercise response could also be excluded from participation. The flow of participants throughout this process is depicted in Figure 1.
Experimental Design

Subjects performed a step-incremental cycling test for determination of \( \dot{V}O_{\text{peak}} \), GET and limit of tolerance (\( T_{\text{lim}} \)) prior to the intervention phase of the study. All subjects completed the same incremental test following the intervention phase and in both cases, this test and measurement of resting metabolic rate (RMR) was done prior to a 10-day controlled feeding period (see below). A timeline depicting this series of events is presented in Figure 2. Pre- and post-intervention testing following the 10-day controlled feeding period included measurements of body composition, insulin sensitivity and substrate utilization. Upon completion of this testing prior to the intervention phase, subjects were randomly assigned to a high-intensity interval training group (HIIT) or a control group (CON). The intervention phase lasted ~14 weeks during which HIIT completed a supervised endurance training intervention (see below) while CON maintained their normal level of physical activity. Both groups received careful monitoring and dietary counseling by a registered dietitian to ensure weight stability throughout the course of the study. With respect to the controlled feeding period, subjects completed the Paffenbarger Physical Activity Questionnaire both prior to and following the intervention phase to account for differences in physical activities of daily living (48). Pre and post insulin sensitivity was assessed during the follicular phase of the menstrual cycle.

Resting Metabolic Rate

Following screening and prior to the step-incremental test, subjects had their RMR measured by indirect calorimetry. Subjects reported to the laboratory between 7:00 and 9:00 AM after a 12-h overnight fast and remained stationary in a supine position for 20 minutes. Exhaled air was then continuously sampled for 40 minutes using a ventilated hood system (Vmax Encore, VIASYS Healthcare Inc, Yorba Linda, CA) to determine the rates of oxygen
consumption ($\dot{V}_o_2$) and carbon dioxide production ($\dot{V}_c_o_2$). $\dot{V}_o_2$ and $\dot{V}_c_o_2$ were averaged for the final 30 minutes of testing and these averages were used to determine RMR, fat oxidation rate (FO) and carbohydrate oxidation rate (CO) using the following stochiometric equations (11, 19):

$$RMR = [(3.58 \times \dot{V}_o_2) + (1.448 \times \dot{V}_c_o_2) - 0.002] \times 4.184 \times 1440$$

(1)

$$FO = (1.67 \times \dot{V}_o_2) - (1.67 \times \dot{V}_c_o_2)$$

(2)

$$CO = (4.55 \times \dot{V}_c_o_2) - (3.21 \times \dot{V}_o_2)$$

(3)

where $\dot{V}_o_2$ and $\dot{V}_c_o_2$ are expressed in L·min$^{-1}$, RMR is expressed in kJ·day$^{-1}$ and FO and CO are expressed in g·min$^{-1}$. For post-intervention RMR, this procedure was repeated on week 12 of the intervention period ≥48 hours following an exercise session.

**Step-incremental Cycling Test**

Before and after the intervention phase, subjects performed a step-incremental cycling test to limit of tolerance on an electronically-braked cycle ergometer (Monarch, 828E, Hasbro, Sweden). For HIIT post intervention, this test took place at least 48 hours following an exercise session. After three minutes of unloaded “warm-up” cycling, work rate (WR) was increased to 25 W and subjects cycled for two minutes at a self-selected cadence (50-70 rpm) after which WR was increased by 15 W per two-minute stage until the limit of tolerance. During these tests, pulmonary gas exchange and ventilation were measured breath by breath using open-circuit spirometry (same system as RMR measurement; see above). The gas analyzers were calibrated before each test with gases of known concentration and the turbine volume transducer was calibrated with a 3-L syringe. Gas exchange and ventilatory data were collected continuously and averaged over consecutive 10-s periods. Heart rate and cardiac function were also recorded continuously via electrocardiogram (Marquette
Electronics, MAC VU, Milwaukee, WI) and blood pressure was measured every two minutes to ensure normal physiological responses.

**Exercise Performance Parameters**

$\dot{V}O_{2\text{peak}}$ was defined as the highest 30-s rolling mean $\dot{V}O_2$ value attained prior to termination of the incremental test. The WR attained during the final stage ($WR_{peak}$) and time to limit of tolerance ($T_{lim}$) was recorded. We also determined the time for which $\dot{V}O_{2\text{peak}}$ could be maintained ($t_{\dot{V}O_{2\text{peak}}}$) by calculating the duration for which 10-s mean $\dot{V}O_2$ values lying within one standard deviation (in relation to the corresponding 30-s rolling mean) of $\dot{V}O_{2\text{peak}}$ appeared consistently (i.e., with $\leq$1 value not satisfying the criterion appearing consecutively). GET was determined by consensus from a panel of independent reviewers experienced at making the determination from a cluster of measurements including: 1.) the first disproportionate increase in $\dot{V}cO_2$ from visual inspection of individual plots of $\dot{V}cO_2$ vs. $\dot{V}O_2$; 2.) an increase in expired ventilation ($\dot{V}E$) /$\dot{V}O_2$ with no increase in $\dot{V}E$ /$\dot{V}cO_2$; and 3) an increase in end-tidal $O_2$ tension with no fall in end-tidal $CO_2$ tension. Once determined, GET was expressed as a metabolic rate both in absolute (i.e., $\dot{V}O_2$ in L·min$^{-1}$) and relative (to $\dot{V}O_{2\text{peak}}$) terms. Finally, $\dot{V}O_2$ and $\dot{V}cO_2$ were averaged over the final 20 seconds of each 2-min stage and these $\dot{V}O_2$ values were used to determine the $\dot{V}O_2$/WR slope via linear regression with the fitting window constrained to all stages that were completed.

**Controlled Feeding Period**

The pre- and post-intervention RMR estimates for each subject (see above) were used to construct a weight-maintaining high-fat diet (50% fat, 35% carbohydrate, 15% protein) with energy content = RMR x 1.5 (NDSR software) (1). This diet was designed to promote maximal stimulation of fat oxidation with weight maintenance (7).
devised the diet for each subject with consideration given to food preferences, allergies and intolerances and all food was provided free of charge for participants. Following the incremental cycling test before and after the intervention phase, subjects ingested this diet during a 10-day controlled feeding period that preceded insulin-sensitivity and substrate-utilization measurements (see below). The subjects were provided with the foods needed to eat at home for eight days. On day 9, subjects reported to the Clinical Research Center and, beginning at 7:00 am, had their 24-hour energy expenditure (TEE_{24}) measured by whole-body room calorimetry (metabolic chamber, St. Luke’s-Roosevelt Obesity Research Center, New York, NY). To ensure eucaloric energy balance and, therefore, weight stability, dietary modifications were made in accordance with this measured value prior to subsequent measurements. Due to concerns regarding “detraining” of the chronic adaptive response for HIIT subjects, post-intervention insulin-sensitivity and substrate-utilization measurements were performed 72 hours following the final training session. Consequently, subjects began the 10-day controlled feeding period seven days prior to the final training session so that the measurement of TEE_{24} on day 9 (see above) was done 48 hours following the final training session. CON subjects were tested according to the same timeline, which is depicted in Figure 2.

**Body-composition Measurements**

Prior to the 10-day controlled feeding period, subjects had their body mass (Weight Tronix, New York, NY) and height (Holtain Stadiometer, Crosswell, Wales) measured to the nearest 0.1 kg and 0.5 cm, respectively. Subjects wore a hospital gown and undergarments for this assessment. Subjects were instructed to carefully monitor their body mass throughout the feeding period and report any changes that they experienced. Dietary adjustments were made for changes >±2 kg. Measurements on day 9 of the controlled feeding period also included
fat mass, fat-free mass and percent body fat (dual x-ray absorptiometry; DXA) and total-body skeletal muscle and site-specific adipose tissue (whole-body multi-slice MRI; 1). Body mass was also measured weekly throughout the intervention phase.

**Insulin-sensitivity Measurement**

Following the controlled feeding period after an overnight fast, subjects were assessed before (i.e., in the post-absorptive state) and during a three-hour euglycemic-hyperinsulinemic clamp. During this procedure, blood samples were collected at 10-minute intervals during the post-absorptive and steady-state conditions and these samples were immediately centrifuged, aliquoted and frozen at -80°C. Plasma insulin concentration was measured by radioimmunoassay (Linco Research, St. Charles, MO), glucose concentration was assessed using the glucose-oxidase method (Beckman glucose analyzer, Fullerton, CA) and the concentration of free fatty acids (FFA) was determined via the enzymatic colorimetric method (Wako Chemicals USA, Richmond, VA). FFA suppression was calculated as the difference between FFA at hyperinsulinemic steady state and FFA during the post-absorptive condition expressed as a percent change relative to the latter. Insulin clearance (IC) was calculated as the ratio of the difference in insulin concentration between hyperinsulinemic-steady-state and post-absorptive conditions vs. the rate of insulin infusion during the procedure (80 mU/m²/min) (16). Whole-body glucose disposal rate (GDR) was determined and expressed relative to FFM (M) after which insulin sensitivity index (i.e., M adjusted for steady-state plasma insulin level; M/I) was calculated.

**Substrate-utilization Measurements**

As was the case for RMR, the ventilated hood system was used to perform indirect calorimetry during the post-absorptive and hyperinsulinemic-steady-state conditions of the
euglycemic clamp. For both conditions, subjects were supine and awake. \( \dot{V}_{O_2} \) and \( \dot{V}_{CO_2} \) measurements were used to estimate rates of substrate oxidation (Equations 2 and 3) and to determine the non-protein respiratory exchange ratio (NPRER; \( \dot{V}_{CO_2}/\dot{V}_{O_2} \)). The change in NPRER between conditions (\( \Delta \text{NPRER} \)) was calculated as a measure of metabolic flexibility. Substrate utilization and NPRER were also determined for the step-incremental test based on \( \dot{V}_{O_2} \) and \( \dot{V}_{CO_2} \) averages for each 2-min stage (see above). These estimates were confined only to work rates that fell below GET for all subjects (i.e., prior to the point at which “non-metabolic” CO\(_2\) appears in the pulmonary gas-exchange signal).

**High-intensity Interval Training Intervention** For the experimental group, the intervention phase involved HIIT sessions performed three times per week for ~14 weeks. (Note: To ensure that post-intervention testing was done during the follicular phase of a subject’s menstrual cycle, the intervention phase was shortened to 13 weeks or extended to 15 weeks if necessary.) All sessions were supervised by an exercise physiologist. The total duration of each session was 24 minutes. Intensity of training was monitored via heart-rate response based on a percentage of heart-rate reserve (HRR; the difference between the maximal and resting heart rates that were measured during the pre-intervention incremental test). Each HIIT session began with six minutes of warm-up cycling at 50% HRR after which four work intervals (30-60 s at 75-90% HRR) were performed with recovery intervals (180-210 s at 50% HRR) interspersed. Following the final work interval, five minutes of “cool-down” cycling was performed. Progressive overload was applied over the course of the intervention by manipulating both work-interval intensity and work/recovery ratio (see Figure 3).

**Statistical Analysis**
An independent *t*-test was used to assess differences between HIIT and CON prior to the intervention phase. A 2 x 2 (time by group) repeated-measures ANOVA was employed to determine the effects of the training intervention on the parameters of interest. Significant effects were further evaluated using post-hoc *t*-tests with the alpha level adjusted via a Fisher’s LSD correction. Data are presented as mean ± SD. Statistical significance was accepted when *P*<0.05.
Results

Fourteen subjects were assigned to HIIT and 14 subjects were assigned to CON; however, five members of HIIT and three members of CON did not complete the study (see Figure 1). The data of these subjects, therefore, were excluded from analysis. Reasons for these dropouts were: 1.) the disruption caused by Hurricane Sandy (HIIT, n = 2); 2.) an inability to satisfy time commitments (HIIT, n = 3; CON, n = 1); 3.) dissatisfaction with the no-exercise/weight-management requirements for the group (CON, n = 1); and 4.) relocation (CON, n = 1). Pre-intervention data for the subjects that did complete the study for HIIT (age, 29 ± 4 yr; fasting blood glucose, 88 ± 13 mg∙dL⁻¹; 2-h OGTT, 104 ± 28 mg∙dL⁻¹; n = 9) and CON (age, 30 ± 7 yr; fasting blood glucose, 93 ± 7 mg∙dL⁻¹; 2-h OGTT, 106 ± 15 mg∙dL⁻¹; n = 11) are presented in Tables 1-3. Physical activities of daily living (Paffenbarger scale) were similar between groups prior to the intervention phase and the values were consistent with what would be expected for sedentary subjects (HIIT, 831 ± 389 kcal/week; CON, 679 ± 466 kcal/week). There were also no significant differences in age, fasting blood glucose, 2-h OGTT, RMR, TEE24, body mass or measures of body composition, exercise performance (except for $\dot{V}O_{2}\text{peak}$ in L∙min⁻¹ and $t\dot{V}O_{2}\text{peak}$, $P<0.05$; see Table 3), insulin sensitivity or substrate utilization ($P>0.05$; Tables 1-3). All subjects fully complied with dietary consultations and weekly weighing throughout the course of the study and all nine members of HIIT completed 100% of the training that was prescribed (eight in an uninterrupted manner, one with a three-week hiatus interspersed). However, two subjects in CON did not undergo pre- or post-intervention clamp testing (veins inaccessible for infusion), two subjects in CON did
not undergo post-intervention MRI testing (discouraged due to discomfort experienced
during pre-test) and one subject in HIIT did not undergo post-intervention exercise
testing (ill the day the test was scheduled and subsequently left the country).
Furthermore, due to poor data collection, the exercise-testing data of another HIIT subject
could not be used. Consequently, data presented for measurements derived during these
tests are based on $n = 9$ for CON (MRI and clamp testing) and $n = 7$ for HIIT (exercise
testing).

**Resting Metabolic Rate and 24-hour Energy Expenditure**

Pre/post RMR estimates (Equation 1) were $1,389 \pm 269$ and $1,466 \pm 209$ kcals·day$^{-1}$ for
HIIT and $1,411 \pm 104$ and $1,454 \pm 187$ kcals·day$^{-1}$ for CON. Pre/post TEE$_{24}$ (metabolic
chamber) was $2,166 \pm 376$ and $2,241 \pm 437$ kcals·day$^{-1}$ for HIIT and $2,003 \pm 207$ and
$2,074 \pm 288$ kcals·day$^{-1}$ for CON. Neither RMR nor TEE$_{24}$ changed over the course of
the intervention phase for either group.

**Body Composition**

Group mean ± SD for body composition measurements are presented in Table 1. As per
the experimental design, body mass did not change in either group during the course of
the study. Fat mass, fat-free mass and percent body fat also did not change significantly
in either group. The volume of visceral adipose tissue was decreased in the HIIT group
($P<0.05$); however, neither the volume of skeletal muscle or subcutaneous, intramuscular
or total adipose tissue was altered by training. There was no change in any tissue-volume
measures in CON.
Insulin Sensitivity

Group mean ± SD for insulin sensitivity measurements are presented in Table 2 and individual-subject responses are depicted in Figure 4 Panel A. There was no group-by-time interaction for the increase in insulin sensitivity that occurred during the intervention phase. IC and FFA suppression during the insulin-stimulated condition were not significantly altered in HIIT or CON.

Substrate-utilization Measurements

Group mean ± SD for substrate-utilization estimates during both conditions of the hyperinsulinemic clamp (post absorptive and insulin stimulated; PA and IS, respectively) and the 40-W stage of the incremental test (i.e., the highest WR for which all subjects were exercising below GET) are provided in Table 2. During the clamp procedure, there were no significant pre/post differences in either post-absorptive or insulin-stimulated NPRER, FO or CO for either group. Consequently, metabolic flexibility (i.e., ∆NPRER) was unaltered by training (see Table 2 and Figure 4 Panel B). However, during the exercise condition, there was a significant group-by-time interaction for NPRER and CO for the 40-W work rate ($P<0.05$) and follow-up analysis revealed that NPRER and CO were reduced in HIIT, but not in CON. FO at 40 W post-training was unaltered by HIIT ($P = 0.06$).

Exercise Performance
Exercise-performance parameters are provided in Table 3. A significant group-by-time interaction was observed for WR_{peak} and T_{lim} (Figure 5) and also for t\dot{V}O_{2peak}, GET absolute and GET relative (P<0.05). Follow-up analysis revealed that these exercise-performance parameters were significantly increased in HIIT, but not in CON (Table 3). Conversely, there was no significant group-by-time interaction for \dot{V}O_{2peak} stated in absolute (Figure 5) terms or when stated relative to total-body or fat-free mass. There was also no change in either group for \dot{V}O_{2}/WR slope.
Discussion

The main findings from this investigation are that a 14-week HIIT intervention without body-weight loss improved metabolic performance during exercise, but not during basal and insulin-stimulated states, in sedentary, premenopausal, non-diabetic, overweight/obese AA women. Specifically, compared to control subjects who performed no exercise training, HIIT subjects experienced reduced CHO oxidation and NPRER at the same absolute submaximal work rate and increased metabolic rate at GET after training. However, fuel oxidation and NPRER under basal and insulin-stimulated conditions during a euglycemic-hyperinsulinemic clamp were unaltered by HIIT, which means that the index we used to assess metabolic flexibility (ΔNPRER) was not influenced by training. HIIT also improved exercise tolerance; however, $\dot{V}O_{2peak}$ was unaffected. These results suggest that compared to the exercise condition, there is greater complexity associated with the metabolic characteristics of fasting and insulin stimulation as assessed in the present study; i.e., basal fat oxidation and insulin-stimulated glucose metabolism/FFA suppression at a saturating insulin dose, respectively. Consequently, these characteristics might only be altered when body-weight loss is also present.

Contrary to our hypothesis, HIIT did not improve insulin sensitivity in at-risk subjects who were not yet diabetic. This contrasts previous reports of improved insulin sensitivity after endurance training in overweight/obese subjects; however, a number of aspects of the present methodology might explain this discrepancy. For example, DeFronzo et al. found increased insulin-mediated glucose metabolism in obese women with normal OGTT after six weeks of traditional endurance training; however, post-training clamp measurements were performed 48-72 hours following the final training session (15).
acute effect of exercise on glucose disposal persists for ~72 hours (38); therefore, this
timing raises concerns that the observed effect might not reflect a chronic adaptation (54).
However, it is also important to ensure that testing is performed prior to dissipation of a
chronic effect; hence, in the present study, we chose to perform post-training
measurements 72 hours following the final training session in an attempt to avoid the
former and include the latter. Questions have also been raised regarding the degree to
which improvements are attributable to exercise training per se, as opposed to altered
energy balance and subsequent weight loss that often accompanies it (53). Consequently,
we rigorously controlled energy balance to ensure weight stability throughout the training
intervention. Our results, therefore, are consistent with the notion that body-weight loss
is a critical component that is required to induce a chronic improvement in insulin
sensitivity. In support of this contention, Schenk et al. report that reductions in systemic
fatty-acid mobilization/uptake due to weight loss play a primary role in increased insulin
sensitivity as the improvement is not amplified when exercise training that enhances the
ability to oxidize fat is also part of the intervention (55).

The exercise program employed in the present investigation might also explain our
findings. Most studies that have assessed the effect of exercise on insulin sensitivity have
used traditional endurance training (i.e., sustainable exercise at a constant work rate for
an extended period). However, heretofore, exercise program variables (e.g., intensity,
duration and volume of training) that optimize benefits have not been well defined. For
example, a cross-sectional analysis across a wide range of ethnicities, ages and glucose-
metabolizing capacities revealed similar effects of non-vigorous and vigorous habitual
activity on insulin sensitivity when energy expenditure was accounted for (44). This
implicates total energy expenditure as opposed to intensity per se as the critical stimulus. Similarly, Houmard et al. found that intensities ranging from 40-80% \( \dot{V}O_{2\text{peak}} \) are all sufficient to elicit an improvement; however, regardless of intensity, a training duration of ~170 minutes/week induced a greater effect compared to ~115 minutes/week (33). In contrast, Kang et al. reported that when energy expenditure was matched, insulin sensitivity was improved following seven exercise sessions performed at 70% \( \dot{V}O_{2\text{peak}} \) for 50 minutes, but not 50% \( \dot{V}O_{2\text{peak}} \) for 70 minutes (35). The reason(s) for these discrepant findings is/are unclear, but might include lack of differentiation between acute and chronic effects and/or the method used to determine insulin sensitivity and/or characteristics of the subjects.

In the present investigation, we showed that a low-volume (3 sessions/week x 4 work-bouts/session x 30-60 s/work-bout), high-intensity (75-90% HRR) interval training program did not improve insulin sensitivity in overweight/obese subjects using the clamp, which is the “gold-standard” means of assessment (8). This contrasts previous reports of a “chronic” (i.e., at 72 hours) improvement in insulin sensitivity in healthy normal-weight subjects after six sessions of SIT (sprint interval training; i.e., HIIT with work intervals performed with “all-out” effort) using the clamp (51) and OGTT (3). However, for overweight/obese men, a similar SIT protocol elicited an acute effect at 24 hours that was no longer present 48 hours later (64). Previous investigations of the influence of HIIT on insulin sensitivity in overweight/obese subjects have also returned equivocal findings (14, 24, 31). Lack of effect in this case has been suggested to reflect a blunted response in females (24) and/or the influence of the diet that accompanied the training (22). Consequently, either of these factors alone or the two in concert might explain why our
HIIT protocol did not improve insulin sensitivity in overweight/obese females who had their diets controlled so that they did not lose body-weight during the intervention. However, with respect to the latter, it is interesting to note that HIIT subjects did experience a ~16% reduction in visceral adipose tissue, which should be linked to improved insulin sensitivity regardless of whether body-weight loss is also present (46). The reason(s) it was not is/are unclear, but might be related to our subject population as greater insulin resistance in AA compared to white women is not related to differences in any of the adipose-tissue compartments including the visceral region (1). Consequently, it is possible that a HIIT program like the present one without weight loss might benefit insulin sensitivity when a more “typical” profile is present (i.e., in populations where visceral adipose tissue plays a predominant role in insulin resistance).

In addition to assessing insulin sensitivity according to glucose disposal rate (both the absolute value and the absolute value adjusted for steady-state insulin level; i.e., M and M/I, respectively), we also assessed insulin’s regulatory influence by measuring the metabolic flexibility observed when switching between conditions where fat and carbohydrate oxidation are preferred. We chose to quantify this capacity by calculating the difference in NPRER between post-absorptive and insulin-stimulated conditions of the clamp (ΔNPRER) and, contrary to our hypothesis, no training-related improvement was observed. Indeed, neither post-absorptive nor insulin-stimulated substrate utilization was favorably altered by HIIT (see Table 2 and Figure 4). This contrasts previous reports by Goodpaster et al. who found that the combination of exercise training and body-weight loss for obese subjects increased both the insulin-stimulated capacity for glucose utilization and the ability to oxidize fat in the basal state. Importantly, improvement of
the latter was associated with increased insulin sensitivity, which highlights the critical influence of insulin action with regard to functional fuel switching.

There are a number of differences between our methodology and that employed in the study of Goodpaster et al. that might explain the discrepant findings regarding post-absorptive and insulin-stimulated substrate oxidation. As previously mentioned, Goodpaster et al. combined exercise with weight loss induced by dietary intervention (26). This is important because Solomon et al. found that after 12 weeks of moderate-intensity endurance training, post-absorptive fat oxidation was increased when accompanied by a hypocaloric, but not a eucaloric diet (56). Similarly, there is no acute effect of eucaloric exercise on fat oxidation (45). Therefore, the lack of effect of HIIT on post-absorptive fat oxidation in the present study might be related to the weight-stability aspect of our methodology. However, it is important to note that the obese subjects trained by Solomon et al. had impaired glucose tolerance, which was not the case for our subjects (57). Moreover, both interventions employed in that study improved insulin sensitivity; therefore, body-weight loss was not required in addition to exercise to elicit an effect. Collectively, this suggests that the pre-training status of our subjects might have also played a role in our findings. For example, given that impaired post-absorptive fat oxidation predicts the severity of insulin resistance (37) and subjects with low rates of post-absorptive fat oxidation improve to a greater extent due to training (26), it is possible that the “window for adaptation” was not sufficiently large for our subjects to benefit from training. Indeed, post-absorptive NPRER for the HIIT group prior to the training intervention in our study (~0.79) was lower than that which was present pre-training for the subjects of Goodpaster et al. and that which has been reported for obese...
metabolically-inflexible individuals (26, 37, 43). Consequently, it appears as if metabolic flexibility in our at-risk subjects was quite high prior to training (e.g., ∆NPRER ≈ 0.14), which means that the present findings cannot be used as conclusive proof that HIIT without body-weight loss does not improve metabolic flexibility in metabolically-inflexible subjects. We also found high rates of insulin-induced FFA suppression pre-training (e.g., ~97% in both groups), which further suggests that our subjects had sufficient metabolic flexibility prior to the intervention. However, the high rates of FFA suppression during the pre-training clamp assessment might also reflect the high rate of insulin infusion that we used during the procedure (see below). Finally, with respect to the smaller window for adaptation that was available for our subjects prior to training, it is important to note that the high-fat controlled diet we had subjects consume might have decreased post-absorptive NPRER causing the “normal” values we observed pre-training and consequent lack of training effect. However, if our subjects were metabolically inflexible due to dysfunctional fat regulation during the post-absorptive state, it should also manifest as an inability to adjust to high-fat intake (60, 62). Indeed, it has been shown that AA women lack metabolic flexibility in response to a high-fat diet regardless of body composition (7).

Much like insulin sensitivity, the HIIT protocol we employed might also explain the disparate findings regarding the effect of training on post-absorptive and insulin-stimulated metabolism. The methodology of Goodpaster et al. resulted in considerable variation in both intensity and duration of exercise during the traditional endurance training that was performed and the authors report that intensity and volume were each
positively correlated with the reduced post-absorptive NPRER (26). Given the nature of HIIT, our subjects performed a much lower volume compared to subjects in that study and while intensity was much higher, traditional endurance training at a sustainable work rate should allow for a greater absolute contribution of fat as fuel. While this might be compensated for by increased energy turnover during the post-exercise recovery period after HIIT (29), it is also possible that sustained exercise at the intensity that elicits the maximal rate of fat oxidation (i.e., “FATmax”) might provide a specific stimulus that is appropriate for obese and/or insulin-resistant subjects (10, 36). Independently or in concert, these unique aspects of HIIT might render it less effective for improving dysfunctional fat metabolism compared to the more traditional approach where a volume threshold is surpassed, but an intensity ceiling is not. Finally, Goodpaster et al. reported a ~20% increase in $\dot{V}_{O_{2\text{max}}}$ due to training whereas in the present study, $\dot{V}_{O_{2\text{peak}}}$ was unaffected by HIIT even though subject adherence to training was high. It is, therefore, possible that the endurance training effect experienced by our subjects was not sufficient to improve post-absorptive fat reliance. However, the possibility that a type II error masked an effect of HIIT on $\dot{V}_{O_{2\text{peak}}}$ in our study cannot be discounted (see below and Figure 5).

Despite no change in substrate utilization at the extremes that were assessed during the clamp procedure, HIIT did result in more favorable fuel selection during exercise at the same absolute submaximal work rate (i.e., 40 W; see Table 2). This is important because use of clamp-derived ΔNPRER as an index of metabolic flexibility is not universally accepted and, indeed, it has been suggested that the flexibility required to adapt to physiological challenges like exercise or meal-to-meal dynamics might provide a better...
indicator (6, 21). A HIIT-induced reduction in exercise NPRER is also important if traditional endurance training at a work rate that requires a high rate of fat oxidation should be incorporated into a HIIT regimen (20). Assessment of metabolic flexibility using post-absorptive NPRER has also been questioned because this value is influenced by acute energy balance and dietary macronutrient consumption (21). To control for this factor, we implemented a 10-day controlled feeding period prior to testing during which subjects ingested a high-fat eucloric diet designed to promote maximal fat oxidation with weight maintenance (7). This diet likely allowed for a consistent comparison across time points.

In addition to fuel utilization at 40 W, a number of other aspects of exercise performance were improved by HIIT. In partial support of our third hypothesis, the metabolic rate at GET was increased in both absolute and relative terms (Table 3). Importantly, this threshold defines a range of metabolic rates for which \( \dot{V}O_2 \) achieves a rapid steady state at the lowest possible oxidative cost and blood-lactate concentration is not elevated above resting level (63). Consequently, while not the maximum sustainable metabolic rate, GET does dictate the highest effort that can be sustained with minimal discomfort (i.e., within the “moderate-intensity domain”). This means that it likely represents a more relevant measure of “functional capacity” for subjects like those in the present study. For example, an increased metabolic rate at GET can support greater functionality during physical activities of daily living and also allow for a higher work rate to be sustained during constant-work-rate “fat-reliant” exercise that might be required for overweight/obese subjects (10, 20).
In further support of our hypothesis, exercise tolerance was increased by HIIT as six of seven subjects exercised for a longer period of time and reached a higher work rate after training (Figure 5, Panel A). However, contrary to our hypothesis, \( \dot{V}O_{2\text{peak}} \) was unchanged (Figure 5, Panel B). One explanation for a higher maximum rate of work with unchanged maximum rate of oxygen consumption is improved exercise economy; however, the \( \dot{V}O_2/\text{WR} \) slope during the incremental protocol was not decreased by training. Training might also improve the ability to persist once \( \dot{V}O_{2\text{peak}} \) is attained and, indeed, we found an approximate two-fold increase in t\( \dot{V}O_{2\text{peak}} \) for HIIT that supports this explanation. Finally, it is possible that a type II error masked the significant improvement in \( \dot{V}O_{2\text{peak}} \) that is typically reported following a HIIT intervention (4). In this regard, \( \dot{V}O_{2\text{peak}} \) was increased in six of seven HIIT subjects (Figure 5, Panel B). Unfortunately, statistical power had been reduced because we only had exercise-test data for seven out of the nine HIIT participants (see above).

A number of methodological aspects of the present study warrant mention. We chose a 14-week training period despite the fact that a number of HIIT studies have shown remarkable training-induced adaptations after much shorter interventions (23). However, given the population we were working with, we were unsure regarding the degree to which we would be able to achieve a sufficient intensity during our work intervals at the beginning of the intervention when subjects were unaccustomed to training. This is why we allowed seven weeks before subjects worked at the highest intensity that was required. We also felt that this gradually-progressing approach might increase the likelihood that subjects would adhere to the program. Finally, we wanted to compare HIIT to the traditional endurance-training interventions that have proven successful at
altering metabolic flexibility (26); hence, we felt a similar intervention length would
better allow us to isolate the effects of the HIIT approach per se. Our HIIT protocol
involving “submaximal” exercise during work intervals was also different from many of
the ones that have been successfully used in healthy subjects where work intervals are
performed with all-out effort (i.e., SIT) (23,51). The insulin infusion rate we chose is
also of note. Insulin resistance in AA women appears to be attributable to lower
peripheral insulin sensitivity as hepatic insulin sensitivity is not different between AA
women and their white counterparts (17). Consequently, to isolate this specific aspect of
metabolic control, we used a saturating dose that would ensure complete suppression of
hepatic glucose production and a blood-glucose “steady state” during the procedure (16).
However, this infusion rate is relatively high, which might explain the near-maximal
values of FFA suppression that were observed pre training and, by extension, the lack of
training-induced change elicited by HIIT. Similarly, sufficient insulin responsiveness
relative to the saturating dose might have masked improvements in insulin sensitivity
(i.e., a leftward shift of the insulin dose-response curve) that occurred due to the training
intervention. Finally, as previously mentioned, it is important to recognize that the
weight-maintenance aspect of our methodology likely influenced our findings.
Consequently, it is important to extend this research by investigating the effects of HIIT
protocols with weight loss allowed in overweight/obese at-risk subjects.

In conclusion, a 14-week HIIT intervention improved metabolic performance during
exercise, but did not improve insulin sensitivity or metabolic flexibility assessed between
basal and insulin-stimulated states during a euglycemic-hyperinsulinemic clamp with
saturating insulin dose in sedentary, premenopausal, non-diabetic, AA women. With
respect to metabolic flexibility, the lack of effect was due to unaltered fat utilization and 
fat suppression during post-absorptive and insulin-stimulated conditions, respectively. 
These lack of improvements likely reflect the fact that body-weight loss did not 
accompany the intervention. Furthermore, while this subject population is at high risk, 
future research should explore the degree to which a similar HIIT intervention might 
 improve these dysfunctional aspects of metabolism in overweight/obese subjects with 
greater disease progression and, therefore, a larger window for adaptation. Future 
research might also investigate ways in which HIIT can be enhanced for 
overweight/obese subjects; e.g., by combining it with traditional endurance training that 
relies on fat as fuel to a greater extent. HIIT also improved exercise tolerance, metabolic 
rate at GET and exercise fat utilization. These changes have both functional importance 
and implications regarding supplemental training that might be required in addition to 
HIIT to restore fuel-regulating capacity in metabolically-inflexible individuals.

Grants
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Disclosures
No conflicts of interest, financial or otherwise, are declared by the authors.

Author Contributions
References


17. DeLany JP, Dubé JJ, Standley RA, Distefano G, Goodpaster BH, Stefanovic-Racic M, Coen PM, Toledo FG. Racial differences in peripheral insulin sensitivity and


**Figure Legends**

**Figure 1:** CONSORT diagram depicting the flow of participants through the various stages of this randomized controlled clinical trial. HIIT, high-intensity interval training group; CON, no-exercise control group.

**Figure 2:** Pre- and post-intervention testing protocol that was employed in this study. RMR, measurement of resting metabolic rate; INC, incremental cycling test to limit of tolerance; TEE24, measurement of 24-hour energy expenditure; DXA, measurement of body composition by dual x-ray absorptiometry; MRI, measurement of body composition by whole multi-slice MRI; Clamp, measurement of insulin sensitivity and substrate utilization by euglycemic-hyperinsulinemic clamp.

**Figure 3:** Exercise programming variables for 14-week HIIT intervention (frequency, 3 sessions/week; intervals, 4 repetitions/session) with progression applied via both work-interval intensity and work/recovery duration ratio. HRR, heart-rate reserve.

**Figure 4:** Group mean ± SD with individual-subject data superimposed for M/I (Panel A) and ΔNPRER (Panel B) before (Pre) and after (Post) intervention phase for high-intensity interval training group (HIIT; left panel) and no-exercise control group (CON; right panel). M/I, whole-body glucose disposal rate adjusted for steady-state plasma insulin level; ΔNPRER, difference in non-protein respiratory exchange ratio between post-absorptive and insulin-stimulated conditions of the euglycemic-hyperinsulinemic clamp.
Figure 5: Group mean ± SD with individual-subject data superimposed for T\textsubscript{lim} (Panel A) and \(\dot{V}o_2\text{peak}\) (Panel B) before (Pre) and after (Post) intervention phase for high-intensity interval training group (HIIT; left panel) and no-exercise control group (CON; right panel). T\textsubscript{lim}, limit of tolerance during incremental cycling test; \(\dot{V}o_2\text{peak}\), peak rate of oxygen consumption. * indicates significant group-by-time interaction for increase in HIIT \((P<0.05)\).
Table 1: Body composition and tissue volumes pre- and post-intervention in the HIIT and CON groups.

<table>
<thead>
<tr>
<th></th>
<th>HIIT Pre</th>
<th>HIIT Post</th>
<th>CON Pre</th>
<th>CON Post</th>
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<tbody>
<tr>
<td><strong>Body Composition</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Body mass (kg)</td>
<td>90.1 ± 13.8</td>
<td>90.2 ± 14.5</td>
<td>85.5 ± 10.7</td>
<td>84.4 ± 10.6</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>32.5 ± 3.6</td>
<td>32.7 ± 3.8</td>
<td>32.1 ± 3.2</td>
<td>31.6 ± 3.6</td>
</tr>
<tr>
<td>Fat mass (kg)</td>
<td>39.3 ± 7.7</td>
<td>38.5 ± 8.9</td>
<td>37.3 ± 7.2</td>
<td>36.7 ± 9.2</td>
</tr>
<tr>
<td>Fat-free mass (kg)</td>
<td>50.3 ± 6.5</td>
<td>50.6 ± 6.2</td>
<td>47.8 ± 5.5</td>
<td>47.7 ± 5.9</td>
</tr>
<tr>
<td>Percent body fat (%)</td>
<td>45.4 ± 3.7</td>
<td>44.5 ± 4.0</td>
<td>45.4 ± 5.0</td>
<td>44.5 ± 8.0</td>
</tr>
<tr>
<td><strong>Tissue Volumes</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Skeletal muscle (L)</td>
<td>24.3 ± 3.5</td>
<td>25.0 ± 3.8</td>
<td>23.9 ± 3.7</td>
<td>24.3 ± 4.0</td>
</tr>
<tr>
<td>Total adipose (L)</td>
<td>40.4 ± 8.7</td>
<td>39.2 ± 9.4</td>
<td>39.3 ± 7.8</td>
<td>38.3 ± 7.4</td>
</tr>
<tr>
<td>Subcutaneous adipose (L)</td>
<td>37.8 ± 8.0</td>
<td>36.8 ± 8.6</td>
<td>36.7 ± 7.5</td>
<td>35.8 ± 7.2</td>
</tr>
<tr>
<td>Visceral adipose (L)</td>
<td>1.3 ± 0.7</td>
<td>1.1 ± 0.6 *</td>
<td>1.3 ± 0.6</td>
<td>1.2 ± 0.6</td>
</tr>
<tr>
<td>Intramuscular adipose (L)</td>
<td>1.3 ± 0.4</td>
<td>1.3 ± 0.3</td>
<td>1.3 ± 0.6</td>
<td>1.3 ± 0.4</td>
</tr>
</tbody>
</table>

Values are mean ± SD. HIIT, high-intensity interval training group; CON, no-exercise control group; BMI, body mass index. *: significant group-by-time interaction for reduction in HIIT \(P<0.05\).
Table 2: Insulin-sensitivity and substrate-utilization measurements pre- and post-intervention for the HIIT and CON groups.

<table>
<thead>
<tr>
<th></th>
<th>HIIT Pre</th>
<th>HIIT Post</th>
<th>CON Pre</th>
<th>CON Post</th>
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<tbody>
<tr>
<td><strong>Insulin Sensitivity</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>IC (mL·m²BSA⁻¹·min⁻¹)</td>
<td>368 ± 42</td>
<td>355 ± 36</td>
<td>404 ± 73</td>
<td>393 ± 92</td>
</tr>
<tr>
<td>M (mg·min⁻¹·kg⁻¹FFM)</td>
<td>14.1 ± 2.5</td>
<td>16.6 ± 4.3</td>
<td>15.2 ± 2.7</td>
<td>16.8 ± 4.4</td>
</tr>
<tr>
<td>M/I (mg·min⁻¹·kg⁻¹FFM/mU·mL⁻¹)</td>
<td>0.06 ± 0.01</td>
<td>0.07 ± 0.03</td>
<td>0.08 ± 0.02</td>
<td>0.08 ± 0.02</td>
</tr>
<tr>
<td>FFA suppression (%)</td>
<td>96.5 ± 1.4</td>
<td>96.8 ± 1.9</td>
<td>96.5 ± 1.9</td>
<td>94.9 ± 3.7</td>
</tr>
<tr>
<td><strong>Post-absorptive Substrate Utilization</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPRERPA</td>
<td>0.79 ± 0.02</td>
<td>0.80 ± 0.04</td>
<td>0.81 ± 0.04</td>
<td>0.80 ± 0.03</td>
</tr>
<tr>
<td>FOPA (mg·min⁻¹·kg⁻¹FFM)</td>
<td>1.36 ± 0.25</td>
<td>1.34 ± 0.35</td>
<td>1.39 ± 0.43</td>
<td>1.45 ± 0.39</td>
</tr>
<tr>
<td>COPA (mg·min⁻¹·kg⁻¹FFM)</td>
<td>1.60 ± 0.39</td>
<td>1.69 ± 0.64</td>
<td>1.92 ± 0.53</td>
<td>1.75 ± 0.56</td>
</tr>
<tr>
<td><strong>Hyperinsulinemic Substrate Utilization</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPRERIS</td>
<td>0.93 ± 0.04</td>
<td>0.95 ± 0.07</td>
<td>0.93 ± 0.05</td>
<td>0.93 ± 0.05</td>
</tr>
<tr>
<td>FOIS (mg·min⁻¹·kg⁻¹FFM)</td>
<td>0.49 ± 0.26</td>
<td>0.37 ± 0.43</td>
<td>0.47 ± 0.37</td>
<td>0.49 ± 0.37</td>
</tr>
<tr>
<td>COIS (mg·min⁻¹·kg⁻¹FFM)</td>
<td>4.27 ± 0.82</td>
<td>4.75 ± 1.16</td>
<td>4.49 ± 1.18</td>
<td>04.78 ± 1.28</td>
</tr>
<tr>
<td><strong>Metabolic Flexibility</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>∆NPRER</td>
<td>0.14 ± 0.04</td>
<td>0.15 ± 0.06</td>
<td>0.13 ± 0.05</td>
<td>0.14 ± 0.05</td>
</tr>
<tr>
<td><strong>Exercise Substrate Utilization</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPRER₄₀</td>
<td>0.93 ± 0.08</td>
<td>0.84 ± 0.06</td>
<td>0.85 ± 0.06</td>
<td>0.91 ± 0.08</td>
</tr>
<tr>
<td>FO₄₀ (mg·min⁻¹·kg⁻¹FFM)</td>
<td>2.18 ± 2.66</td>
<td>4.42 ± 2.82</td>
<td>2.81 ± 1.13</td>
<td>1.81 ± 2.17</td>
</tr>
<tr>
<td>CO₄₀ (mg·min⁻¹·kg⁻¹FFM)</td>
<td>16.33 ± 8.12</td>
<td>10.01 ± 5.65</td>
<td>8.49 ± 5.14</td>
<td>12.74 ± 7.75</td>
</tr>
</tbody>
</table>

Values are mean ± SD. HIIT, high-intensity interval training group; CON, no-exercise control group; IC, insulin clearance; M, whole-body glucose disposal rate; M/I, whole-body glucose disposal rate adjusted for steady-state plasma insulin level; FFA, free fatty acid; ∆NPRER,
difference in non-protein respiratory exchange ratio between post-absorptive and insulin-
stimulated conditions of the euglycemic-hyperinsulinemic clamp; FO, fat oxidation; CO,
carbohydrate oxidation; subscript PA, post absorptive; subscript IS, insulin stimulated; subscript
40, cycling at 40 W. *: significant group-by-time interaction for reduction in HIIT ($P<0.05$).

Table 3: Exercise performance parameters pre- and post-intervention in the HIIT and
CON groups.

<table>
<thead>
<tr>
<th></th>
<th>HIIT Pre</th>
<th>HIIT Post</th>
<th>CON Pre</th>
<th>CON Post</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\dot{V}O_2\text{peak}$ (L·min$^{-1}$)</td>
<td>$2.18 \pm 0.47 \dagger$</td>
<td>$2.30 \pm 0.45$</td>
<td>$1.68 \pm 0.49$</td>
<td>$1.78 \pm 0.48$</td>
</tr>
<tr>
<td>$\dot{V}O_2\text{peak}$ (mL·min$^{-1}$·kg$^{-1}$)</td>
<td>$23.1 \pm 4.9$</td>
<td>$24.9 \pm 5.5$</td>
<td>$19.7 \pm 6.3$</td>
<td>$20.9 \pm 4.6$</td>
</tr>
<tr>
<td>$\dot{V}O_2\text{peak}$ (mL·min$^{-1}$·kg$^{-1}$·FFM)</td>
<td>$42.1 \pm 7.1$</td>
<td>$45.1 \pm 9.1$</td>
<td>$35.1 \pm 10.3$</td>
<td>$37.6 \pm 9.9$</td>
</tr>
<tr>
<td>$WR_{\text{peak}}$ (W)</td>
<td>$139 \pm 15$</td>
<td>$156 \pm 26 \ast$</td>
<td>$137 \pm 18$</td>
<td>$133 \pm 22$</td>
</tr>
<tr>
<td>$T_{\text{lim}}$ (s)</td>
<td>$987 \pm 146$</td>
<td>$1124 \pm 202 \ast$</td>
<td>$972 \pm 146$</td>
<td>$931 \pm 173$</td>
</tr>
<tr>
<td>$t\dot{V}O_2\text{peak}$ (s)</td>
<td>$41 \pm 12 \dagger$</td>
<td>$86 \pm 40 \ast$</td>
<td>$76 \pm 35$</td>
<td>$58 \pm 25$</td>
</tr>
<tr>
<td>GET absolute (L·min$^{-1}$)</td>
<td>$0.97 \pm 0.23$</td>
<td>$1.29 \pm 0.34 \ast$</td>
<td>$0.87 \pm 0.35$</td>
<td>$0.91 \pm 0.37$</td>
</tr>
<tr>
<td>GET relative (%$\dot{V}O_2\text{peak}$)</td>
<td>$45 \pm 6$</td>
<td>$56 \pm 7 \ast$</td>
<td>$51 \pm 15$</td>
<td>$50 \pm 12$</td>
</tr>
<tr>
<td>$\dot{V}O_2/WR$ slope (mL·min$^{-1}$·W$^{-1}$)</td>
<td>$12.9 \pm 2.6$</td>
<td>$13.3 \pm 3.7$</td>
<td>$10.4 \pm 5.0$</td>
<td>$9.9 \pm 3.5$</td>
</tr>
</tbody>
</table>

Values are mean ± SD. HIIT, high-intensity interval training group; CON, no-exercise control
group; $\dot{V}O_2\text{peak}$, peak rate of oxygen consumption; $WR_{\text{peak}}$, peak rate of work; $T_{\text{lim}}$, limit of
tolerance; $t\dot{V}O_2\text{peak}$, time for which the peak rate of oxygen consumption could be maintained; GET,
gas exchange threshold; $\dot{V}O_2/WR$ slope, the slope of the relationship between rate of oxygen
consumption and rate of work during incremental cycling. *: significant group-by-time interaction
for increase in HIIT ($P<0.05$). † significant difference for pre-intervention values between groups
($P<0.05$).
Assessed for eligibility ($n = 490$)

Consented ($n = 98$)

Passed initial screening ($n = 40$)

Randomized ($n = 28$)

Excluded ($n = 392$):
- failed to meet inclusion criteria

Excluded ($n = 58$):
- declined participation
- failed to meet inclusion criteria
- lost to follow-up

Excluded ($n = 12$):
- declined participation
- lost to follow-up
- abnormal ECG during incremental test

Allocated to HIIT ($n = 14$)

Allocated to CON ($n = 14$)

Dropouts ($n = 5$):
- Hurricane Sandy
- time commitment

Completed intervention phase ($n = 9$)

Completed intervention phase ($n = 11$)

Dropouts ($n = 3$)
<table>
<thead>
<tr>
<th>Work Interval</th>
<th>75% HRR</th>
<th>80% HRR</th>
<th>85% HRR</th>
<th>90% HRR</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 s</td>
<td>45 s</td>
<td>60 s</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Rest Interval</th>
<th>50% HRR</th>
</tr>
</thead>
<tbody>
<tr>
<td>210 s</td>
<td>195 s</td>
</tr>
<tr>
<td>180 s</td>
<td></td>
</tr>
</tbody>
</table>
Δ NPRER

HIIT

CON

M/I (mg·kg⁻¹·min⁻¹·m⁻¹·mL⁻¹)

Pre                       Post

Pre                       Post

Δ NPRER

Pre                       Post

Pre                       Post
A

HIIT

CON

$T_{lim}(s)$

Pre                   Post

Pre                   Post

*  

0.0  0.5  1.0  1.5  2.0  2.5

0  800  1000  1200  1400

B

$\dot{V}O_{2peak}(L \cdot min^{-1})$

Pre                   Post

Pre                   Post