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Title:

Effects of different aerobic exercise programs with nutritional intervention in sedentary adults with overweight/obesity and hypertension: EXERDIET-HTA study

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Disclosure

The authors have reported no conflict of interest.

Word count: 5085 (including references)

Abstract

Background: Both exercise training and diet are recommended to prevent and control hypertension (HTN) and overweight/obesity.

Purpose: To determine the effectiveness of different 16-week aerobic exercise programs with hypocaloric diet on blood pressure (BP), body composition, cardiorespiratory fitness (CRF) and pharmacological treatment.

Methods: Overweight/obese, sedentary participants (n=175, 54.0±8.2 yrs) with HTN, were randomized into attention control group (AC, physical activity recommendations) or one of three supervised exercise groups [two days/week: high-volume with 45 min of moderate-intensity continuous training (HV-MICT), HV and high-intensity interval training, alternating high and moderate intensities (HV-HIIT), and low volume-HIIT (LV-HIIT, 20 min)]. All variables were assessed pre and post intervention. All participants received the same hypocaloric diet.

Results: Following the intervention, there was a significant reduction in BP and body mass in all groups with no between-group differences for BP. However, body mass was significantly less reduced in the AC group compared with all exercise groups (AC=-6.6%, HV-MICT=-8.3%, HV-HIIT=-9.7%, LV-HIIT=-6.9%). HIIT groups had significantly higher CRF than HV-MICT, but there were no significant between-HIIT differences (AC=16.4%, HV-MICT=23.6%, HV-HIIT=36.7%, LV-HIIT=30.5%). Medication was removed in 7.6% and reduced in 37.7% of the participants.

Conclusions: The combination of hypocaloric diet with supervised aerobic exercise 2 days/week offers an optimal non-pharmacological tool in the management of BP, CRF and body composition in overweight/obese and sedentary individuals with HTN. HV-HIIT seems to be better for reducing body mass compared to LV-HIIT. The exercise-induced improvement in CRF is intensity dependent with LV-HIIT as a time-efficient method in this population.

Trial Registration: NCT02283047

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Keywords: Obesity; hypertension; high-intensity interval training; low-volume training; blood pressure; cardiorespiratory fitness; body composition

Introduction

Due to the recent changes in both eating habits and lifestyles (*i.e.,* the abandonment of traditional dietary patterns and culinary techniques, increased sedentary time, and decreased volume and intensity of physical activity, which results in an imbalance in the energy balance), primary hypertension (HTN), overweight/obesity, and being sedentary often coexist in the same person.[1,2] Obesity has been considered the driving force of this response culminating in a significant increase in direct and indirect healthcare costs.[3] It is, therefore, important to develop cost-effective strategies for the treatment of obesity in order to reduce the prevalence of obesity-related HTN.[2,4] The European Societies of Hypertension (ESH) and Cardiology (ESC) recommend appropriate lifestyles changes for the prevention and treatment of HTN, alongside the use of drug therapy in individuals at a high risk.[5] One benefit of losing body mass is the concomitant reduction in blood pressure (BP),[2,3,5] especially in individuals taking antihypertensive medication.[6] Although individual BP responses to a reduced body mass are variable depending on "fat-sensitive" or "fat-resistant" BP,[1] it has been demonstrated that combining exercise and diet may be the most effective treatment for reducing body mass. Consequently, the combination appears to be a logical step in facilitating a substantial improvement in cardiometabolic health, including HTN.[2,5]

During the last two decades, several studies have shown the effectiveness of adherence to the Dietary Approaches to Stop Hypertension (DASH) dietary pattern.[4,7,8] In a population with HTN, the combination of DASH diet with aerobic exercise has resulted in a greater reduction in BP and improved cardiovascular biomarkers than DASH diet alone.[9] Exercise guidelines recommend that both moderate-intensity and high-intensity aerobic training should be used to treat and reduce HTN.[5] However, there is currently no agreement with respect the optimal *F*requency, *I*ntensity, *T*ime, and *T*ype (FITT principle) of exercise prescription.[10] Previously, aerobic high-intensity interval training (HIIT) produced a significant improvement in BP and cardiorespiratory fitness (CRF) compared to moderate-intensity continuous training (MICT).[11-13] Additionally, a dose-response curve for physical activity volume and intensity has previously been reported, this is especially important for sedentary individuals and those with moderate level of physical condition,[14] suggesting that "*some is good but more is better.*" There is also evidence to support the use of low-volume HIIT (LV-HIIT) (*i.e.,* ≤10 min of high-intensity effort) *vs.* high-volume (HV) as a potent and time-efficient training method suggesting "*less is more*".[15]

Currently, no research has determined the effects of different exercise intensities and volumes combined with a hypocaloric diet intervention in overweight/obese, sedentary adults diagnosed with HTN. Therefore, the aim of this study was to determine changes in BP, body composition, CRF and pharmacological treatment following three different (HV-MICT, HV-HIIT, LV-HIIT) 16-week aerobic exercise programs performed twice a week, all combined with hypocaloric diet.

Methods

Study design

EXERDIET-HTA study is a multi-arm parallel, randomized, single-blind controlled experimental trial comparing the effects of different 16-weeks aerobic exercise programs (performed two days per week) combined with a dietary intervention in sedentary, overweight/obese individuals suffering HTN (www.clinicaltrials.gov, number NCT02283047). The study protocol was approved by The Ethics Committee of The University of the Basque Country (UPV/EHU, CEISH/279/2014) and Clinical Investigation of Araba University Hospital (2015-030), and all participants provided written informed consent before any data collection. Medical staff were blinded to the participant randomization process. The design, selection criteria, and procedures for the EXERDIET-HTA study have been previously detailed.[16]

Participants

One hundred and seventy-five non-Hispanic white participants (n=120 men and n=55 women) were enrolled in the study from September 2013 to June 2016 in Vitoria-Gasteiz (Basque Country, Spain). Figure 1 presents a flow diagram of the study process. All participants were classified as overweight (body mass index, BMI>25 $kg \cdot m^{-2}$) or obese (BMI>30 $kg \cdot m^{-2}$)[3] and diagnosed with stage 1 or 2 HTN, defined as a systolic blood pressure (SBP) of 140-179 mmHg and/or a diastolic blood pressure (DBP) of 90-109 mmHg and/or under antihypertensive pharmacological treatment.[5] Physical activity behavior was determined by the International Physical Activity Questionnaire (IPAQ), and only participants who did not comply with the *"Global Recommendations on Physical Activity for Health"*[17] by the World Health Organization were selected.

Measurements

The measurements for the study were taken pre (T0) and post (T1) each 16-week intervention period.

Blood Pressure. Ambulatory BP monitoring (ABPM) was conducted over a 24 hour period using an oscillometric ABPM 6100 (Welch Allyn, New York City, NY, USA) device to evaluate BP in line with the guidelines set by the ESH/ESC.[5] Blood pressure (ABPM) values are displayed as the mean of the day.

Cardiorespiratory fitness. A cardiopulmonary exercise test (CPET) was used to determine peak oxygen uptake ($\dot{V}O_{2peak}$) and ventilatory thresholds (VT). The CPET was performed on an electronically braked Lode Excalibur Sport Cycle Ergometer (Groningen, The Netherlands). The test protocol started at ~70 rpm and 40W, with gradual increments of 10W every minute applied until volitional exhaustion occurred. Continuous electrocardiogram monitoring was conducted throughout each test. Expired gas analysis was assessed using a commercially available metabolic cart (Ergo CardMedi-soft S.S, Belgium Ref. USM001 V1.0). Achievement of $\dot{V}O_{2peak}$ criteria has been previously defined.[18] Ventilatory thresholds (*i.e.,* VT1 and VT2) were assessed by standardized methods using the ventilatory equivalents.[18] After completion of the test, participants remained stationary on the bike for five minutes recovery with electrocardiogram and BP monitoring throughout. The identification of the two VT determined the three different exercise intensity domains, or ranges for the exercise intervention design (*i.e.,* R1, **light** to moderate; R2, **moderate** to high; R3, **high** to severe).[18]

Dietary assessment. Habitual food consumption and nutrient intake were evaluated using three questionnaires: dietary history, food frequency questionnaire and two face-to-face non-consecutive 24-h recalls. Trained dieticians conducted the necessary correction for within-subject variability in nutrient intake.[19] All nutritional data were calibrated in the Easy Diet computer program. Resting energy expenditure was calculated by the Mifflin St Jeor equation, which has previously been deemed the most appropriate for individuals who are overweight or obese.[20]

Medication. Prescribed medications were recorded and classified into the groups: angiotensin-converting-enzyme inhibitors (ACEI), angiotensin II receptor blockers (ARB), diuretics, calcium channel blockers (CCB,) beta-blockers (BB), statins, hypoglycemic agents, antiplatelets, and anticoagulants. Medical staff controlled all necessary changes to medication pre, during and post-intervention.

Intervention

All participants underwent a hypocaloric diet. Following baseline data collection, participants were randomly allocated to one of the four intervention groups: the Attention Control (AC) group, or the three supervised exercise groups (HV-MICT, HV-HIIT, or LV-HIIT). Each group was stratified by gender, SBP, BMI, and age. All participants were asked to continue with their normal physical activity patterns outside of the study protocol. However, in addition to treatment for the hypocaloric diet, the AC received the standard guidelines for physical activity recommendations in order to comply with ethical procedures regarding health.[5]

Intervention procedures. All exercise groups trained for two nonconsecutive days per week under the supervision of exercise specialists. All sessions started and finished with BP monitoring, and training intensity was dictated by individual heart rate (HR) responses (Polar Electro, Kempele, Finland) and rate of perceived exertion (Borg's 6-20 point). Each session included a 5-10 min warm-up and a 10 min cool-down. The core part of each training session consisted of a range of aerobic exercises; *i.e.,* one day of the week on the treadmill, and the second one on the bike (BH Fitness equipment™). The HV-MICT group performed 45 min aerobic exercise, whereas the HV-HIIT and LV-HIIT conducted 45 and 20 min, respectively. The intensity was individually tailored to each participant's HR at moderate (R2) or vigorous intensities (R3), adjusting the speed and/or incline of the treadmill or the power and speed on the exercise-bike. The rationale of mixing stationary exercise-bike and treadmill was to avoid the osteoarticular impact of two treadmill days taking into account the nature of the HIIT program and the impact derived from overweight/obese participants. The HV-MICT group performed 45 min continuous steady training at R2. Supervised exercise-training protocols have been previously explained in full.[16]

Considering the average $\dot{V}O_{2peak}$ at baseline for all participants (2.01 ± 0.5 L·min^{-1}), the total work performed by the three exercise groups was calculated using the $\dot{V}O_2$-time relationship. As such, the moderate intensity at R2 was taken as 65% of $\dot{V}O_{2peak}$ (1.3 L·min^{-1}) and the high intensity at R3 as 90% of $\dot{V}O_{2peak}$ (1.8 L·min^{-1}). Thus, the HV-MICT performed 45 min at R2 twice per week representing ~117 L. The HV-HIIT performed 45 min twice per week, one day on the treadmill (4x4 min at 1.8 L·min^{-1} at R3 and 29 min at 1.3 L·min^{-1} at R2, representing ~66.5 L), and one day on the exercise-bike (18x30 s at R3 and 36 min at R2 representing ~63 L·min^{-1} resulting a total work of ~129.5 L). The LV-HIIT group performed 20 min twice per week, exercising one day on the treadmill (2x4 min at R3 and 12 min at R2 representing ~30 L) and one day on the exercise-bike (9x30 s at R3 and 15:30 min at R2 representing ~28 L resulting a total work of ~58 L). A criterion for completing the study was set at 100%. Thus, all participants in the supervised-exercise groups performed 32 sessions; if a session was missed (a maximum of four were allowed), these were added on to the end of the 16-week program, maintaining the two sessions per week.

Diet intervention. Hypocaloric and controlled sodium diet (3-6 g/d) was prescribed for each participant. The diet was designed to provide 25% less energy than their daily energy expenditure and to achieve a weekly loss in body mass of between 0.5 and 1.0 kg in accordance with the recommendations of the American Diabetes Association and the Spanish Society for the Study of Obesity.[21] The diet contained ~30% fat, 15% protein, and 55% carbohydrates and was designed in accordance with the DASH diet.[7] Every two weeks participants were weighed and received encouragement and advice alongside nutritional counseling in order to aid compliance.

Statistical analysis

Descriptive statistics were calculated for all variables. Data are expressed as mean±standard deviations (SD) and the range. All variables that were not normally distributed using a Kolmogorov-Smirnov test and so they were log transformed prior to any analysis. Analysis of variance (ANOVA) was used to determine if there were significant pre-intervention between-group differences. The comparison of frequencies in categorical variables among groups was performed using Chi-Square test. A 2 sample *t*-test was used to determine whether there was a significant difference in the recorded data between pre and post intervention within each group. Analysis of covariance (ANCOVA) was used to examine the delta (Δ) score for each group (AC, HV-MICT, HV-HIIT, LV-HIIT), adjusting for age, sex, changes in body mass and the initial value of each of the dependent variables. Helmert contrasts were performed to analyse the difference between the three exercise groups pooled together and AC group. Bonferroni correction was used to determine the level of significance when a significant main effect was found. Data were analyzed according to the intention-to-treat principle. Statistical significance was set at $P<0.05$. All statistical analyses were performed with the SPSS version 22.0. Power calculation was completed using G*Power 3 analysis program.[22] The required sample size was determined for the primary outcome variable (SBP). It was identified that adequate power (0.80) to evaluate differences in our design consisting of four experimental groups would be achieved with 164 people (41 each group, $\alpha=0.05$, effect size f=0.27) based on the pilot study with an SD of 9 mmHg.

Results

Baseline characteristics. Participants and medications were classified by groups and presented in Table 1. Baseline data for all participants have been previously published.[23] At baseline, 86.9% of participants were taking medication irrespective of group. The percentage of participants who took one, two, three or >four medications were 40%, 26.3%, 13.1% and 7.4%, respectively. With respect to medication type, 32.3% of participants took ACEI, 41.1% ARB, 34.3% diuretics, 15.4% CCB, 9.8% BB, 13.7% statins, 6.3% hypoglucemic, 4.6% antiplatelets, and 1.1% anticoagulants. There were no significant between-group differences observed for anthropometric, body composition, hemodynamic, cardiorespiratory and pharmacological treatment at baseline. No major complications or cardiac events occurred during any part of the study.

Physiological changes (Table 2). Following the 16-week intervention, resting SBP, DBP, mean BP and HR decreased ($P<0.05$). Further, in all groups, CRF expressed as $\dot{V}O_{2peak}$ (L min^{-1}) (AC, Δ=10%; $P<0.05$; HV-MICT, Δ=15%; HV-HIIT, Δ=25%; and LV-HIIT, Δ=25%; $P<0.001$), $\dot{V}O_{2peak}$ (mL kg^{-1} min^{-1}) and METs ($P<0.001$) increased. All groups increased at least one MET (Table 2 and Figure 2). However, at VT1 and VT2 (mL kg^{-1} min^{-1}) improvements were observed in HV-HIIT for VT1 ($P=0.003$) and both HIIT exercise groups for VT2 (HV-HIIT, $P<0.001$ and LV-HIIT, $P=0.016$). In contrast, no significant changes were seen in the AC and HV-MICT groups for either VT1 or VT2. Following Bonferroni correction, there were no significant between group differences in any hemodynamic variables (*i.e.,* BP and HR) (Table 2). However, AC showed a smaller but significant improvement in $\dot{V}O_{2peak}$ (P<0.001) compared with all exercise groups (HV-MICT, mean difference=0.606, 95% CI=-2.193-3.405 mL kg^{-1} min^{-1}; HV-HIIT, mean difference=3.215, 95% CI=0.418-6.012 mL kg^{-1} min^{-1}; and LV-HIIT, mean difference=2.846, 95% CI=0.082-5.610 mL kg^{-1} min^{-1}) and MET (P<0.001). Furthermore, both HIIT groups, showed a greater (P=0.008) $\dot{V}O_{2peak}$ and MET (P=0.018) than HV-MICT. In contrast, there were no significant between group differences in any VT variables.

Anthropometric and body composition (Table 2). Following 16-weeks intervention body mass, BMI, waist and hip circumferences, waist-to-hip ratio (WHR), and fat body mass (FBM) decreased (P<0.05) in all groups. In addition, fat-free mass (FFM) and FFM/FBM ratio increased (P<0.05). Following Bonferroni correction, there were significant between-group differences in anthropometric and body composition. The AC had a smaller body mass reduction (T0 *vs.* T1 difference%, Δ=-6.6%; P=0.029) and change in BMI (Δ=6.7%; P=0.030) compared to those in all exercise groups: HV-MICT (Δ=-8.3%), HV-HIIT (Δ=-9.7%) and LV-HIIT (Δ=-6.9%). Further, HV-HIIT had a greater reduction in body mass (P=0.011, mean difference=2.436, 95% CI=-4.972-0.099 kg) and BMI (P=0.015, mean difference=0.805, 95% CI=-0.066-1.675 kg·m^{-2}) compared with LV-HIIT. However, there were no significant between-group differences observed for WHR. With respect to body composition, there were no significant differences in %FFM between AC and all exercise groups (Δ=4.0%; P=0.062): HV-MICT (Δ=6.2%), HV-HIIT (Δ=6.8%) and LV-HIIT (Δ=4.6%). However, the %FFM gain in the HV-HIIT was greater than the AC (P=0.039) group. Similarly, there were no significant differences in %FBM when exercise groups were compared together with AC (Δ=-8.1%; P=0.062): HV-MICT (Δ=-11.3%), HV-HIIT (Δ=-14.1%) and LV-HIIT (Δ=-9.6%). However, HV-HIIT resulted in a greater reduction of %FBM than the AC group (P=0.038).

Pharmacological therapy. Following the 16-week intervention, medication was reduced from 86.9% to 79.3%. Further, 37.7% of participants, which still took medication, had their dose reduced. The percentage of participants who took one, two, three or more than four medications was also reduced to 35.4%, 29.9%, 8.5% and 5.4%, respectively. Specifically, 32.3% of participants took ACEI, 39 % ARB, 30.5% diuretics, 15.2% CCB, 6.1% BB, 11.0% statins, 6.7% hypoglucemic, 3.7% antiplatelets, and 1.2% anticoagulants. Chi-square test revealed that there were no significant between-group differences in medication reduction.

Discussion

To our knowledge, this is the first known study to investigate the impact of exercise programmes, which use different intensities and volumes in conjunction with a dietary intervention in overweight/obese, sedentary adults diagnosed with HTN. The main findings of the study were: 1) all groups significantly improved BP, CRF, body composition following 16-weeks intervention; 2) a substantial decrease of pharmacological treatment was observed; 3) hypocaloric diet and two days of supervised exercise showed improved body mass and CRF compared to a diet only intervention (AC group), but no significant between group differences were observed in BP; 4) the HV-HIIT exercise elicited a greater improvement in body mass and body composition than the LV-HIIT exercise, and 5) the exercise-induced improvement in CRF is more dependent on intensity than volume.

In this study, a 16-week lifestyle intervention significantly improved cardiovascular risk factors (*i.e.,* BP, CRF, and adiposity) in all groups and pharmacological therapy was largely reduced or removed completely. Hence, the hypocaloric DASH diet along with both supervised aerobic exercise and no supervised physical activity recommendations could offer an optimal non-pharmacological tool in the management of HTN. As such, this could result in a cost-effective model for cardiovascular disease prevention[8] and healthcare cost reduction. These results corroborate those of previous investigations that suggested overweight/obese people with above-normal BP could improve BP, and body mass, vascular and autonomic function when they combine exercise and DASH diet with calorie restriction.[9,24] Further, we provide evidence that the combined effects of physical activity and hypocaloric diet enhance BP and reduce the need for pharmacological therapy.[25] To this end, contrary to our hypothesis, all supervised exercise groups had a reduced BP similar to the AC group post intervention (7-9 mmHg in SBP and 3-5 mmHg in DBP). As such, the potential of the DASH diet to elicit significant improvements in SBP and DBP in individuals with HTN who are overweight/obese is confirmed,[8] and it appears to be independent of the FITT principle. However, the lack of between-group differences in BP in the current study could in part be explained by 1) the role physical activity plays in augmenting baroreflex dysfunction, which may result in a reduced sympathetic outflow with a lowered BP and HR response,[26,27] 2) the different exercise interventions appear to be medication dependent with similar BP reduction following all exercise intensities (*i.e.,* MICT or HIIT);[11] and 3) two days of supervised exercise may not be enough to differentiate between exercise modalities over the 16-week period. Previously, it has been reported that there is greater antihypertensive effect seen in response to high-intensity exercise when compared to lower exercise intensities.[11] Previous research found that HIIT three times a week elicited greater significant reductions in BP than MICT and a control group following a 12-week intervention.[12] However, it should be noted that participants using the antihypertensive drug in the mentioned study performed a wash-out before inclusion and so a greater effect may have been seen.

To achieve a negative energy balance is to challenge and target specific pathways in order to produce beneficial changes in the pathogenesis of obesity-related HTN.[2] In the present study, despite the antihypertensive medication and the metabolic potential side effects,[1,4] a dual treatment of hypocaloric diet combined with supervised exercise twice a week was the optimal way to reduce body mass compared to AC. More specifically, HV-HIIT significantly enhanced body mass reduction (kg, ↓9.7%), and fat distribution the most

(%FFM=↑6.8 and %FBM=↓14.1). Given that, HV-MICT and LV-HIIT exercise programs were performed with the same frequency but a reduced intensity and volume, respectively, the improvements seen in HV-HIIT compared to the other two exercise programs were likely caused by enhanced energy expenditure. These data suggest that sedentary people with overweight/obesity and HTN can adapt and respond to exercise training during an energy deficit program with a dose-response curve related to volume and intensity. Furthermore, it has been shown that high levels of moderate-to-vigorous-intensity physical activity are associated with long-term body mass loss maintenance,[28] despite the probable adaptive metabolic response caused by the compensatory down-regulation in resting energy expenditure following exercise-induced body mass loss.[29]

Cardiorespiratory fitness is an independent predictor of all-cause and disease-specific mortality in various populations irrespective of BMI.[30] Thereby; the fat-but-fit paradigm has been given much attention with respect to reducing the risk of illness and death.[31,32] Thus, in the present study (Table 1), while all participants were overweight/obese and considered unfit at baseline with CRF classified as poor (<24.4 mL kg^{-1} min^{-1} in men and <19 mL kg^{-1} min^{-1} in women),[23,33] following the 16-week intervention CRF was improved and classified as "fair-good".[33] Further, all groups improved by at least 1 MET (Figure 2) during the course of the intervention. As such, although participants were still classified as overweight their CRF increased by 16-36%, which is associated with a considerable improvement in cardiovascular risk and reduced all-cause mortality.[34] In addition, the magnitude of change in CRF improvement was significantly different between exercise groups. Specifically, both HIIT programmes elicited significantly greater improvements in CRF than the HV-MICT and AC (Table 2 and Figure 2) groups. Additionally, HIIT groups showed significant improvements in submaximal variables such as VT (Table 2). These enhanced improvements in CRF may be due to stress adaptations, which have been previously shown to cause notable cellular, vascular and metabolic adaptations during HIIT.[35] One remarkable finding of the present study was that

HIIT improved CRF irrespective of the training volume (LV *vs.* HV). Our findings reinforce previous studies, which suggest LV-HIIT is a time-efficient and effective protocol in clinical populations answering the question "Can less be more?[36,37] As such, it may be that LV-HIIT is more appealing for individuals who do not have enough time to train for long periods, or for those who have medical conditions which prevent them from performing exercise for prolonged periods of time.[13,35] However, taking into account the urgent need of increasing caloric expenditure and CRF in this population, LV-HIIT could be an option to tailor supervised exercise along with daily recommendations of lower intensities physical activities.[38]

Although the current study has provided clear evidence for the benefits of combining a hypocaloric DASH diet with exercise, there are some limitations which should be considered: 1) though every effort was made to manage unsupervised time, physical activity performed by participants in AC could not be controlled, and 2) it is difficult to regulate and monitor the adherence of participants to the diet.

Conclusions

In summary, the present study has shown that the combination of hypocaloric DASH diet with different supervised aerobic exercise programs twice a week offers an optimal non-pharmacological tool in the management of risk factors in sedentary individuals with overweight/obesity and HTN. Benefits include an enhanced control of BP, body mass composition, CRF and pharmacological treatment. A dose-response curve related to volume and intensity in the form of 2-weekly bouts of HV-HIIT provided significantly greater reductions in body mass compared to LV. However, the key to enhancing CRF in this population appears to be linked with exercise intensity irrespective of duration. As such, LV-HIIT may be a time-efficient and effective method of improving health.

Author contribution

SMM conceived the study, acquisition of data and drafted the manuscript. IGA contributed to the design, intervention of exercise, acquisition, and analysis of data and drafted the manuscript. PC and AMAB contributed to the design, intervention of exercise, and acquisition of data. JPA and GRA are members of the medical staff. SMF drafted the manuscript. All the authors critically reviewed the manuscript, gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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