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ORIGINAL ARTICLE

The Effects of Prescribed and Self-Paced High-Intensity Interval Exercise on Affective and Enjoyment Responses in Adults with Overweight-to-Obesity

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ABSTRACT

Background. Affective responses (pleasure or displeasure feelings) to high-intensity interval exercise (HIIE) are dependent on the intensity of the work-interval phases, but current evidence is limited to the prescribed-based HIIE protocol (P-HIIE) in overweight and obese adults. The influence of the self-paced HIIE protocol (S-HIIE) on perceptual responses (affective, enjoyment, and perceived exertion) is currently unclear. **Objectives.** This study examined perceptual responses to S-HIIE and P-HIIE in adults overweight and with obesity. **Methods.** Twenty-four overweight and obese men and women (8 men and 16 women; mean ± SD: age = 26.7 ± 0.3 years; body mass index= 26.9 ± 3.7 kg.m-2) were randomized to P-HIIE (n=12; 6×1-min work-intervals at 90% of maximal aerobic speed) or S-HIIE (n=12; 6×1-min work-intervals at self-paced intensity) groups. P-HIIE and S-HIIE work intervals were separated by 75 s recovery. Perceptual responses were recorded before (affective), during (affective and perceived exertion), and after (enjoyment) all conditions. **Results.** S-HIIE elicited greater affect responses across all work intervals compared to P-HIIE (all $P < 0.03$, all effect size (ES) > 0.66), but no post-enjoyment differences were evident in both conditions (P=0.42, ES=0.40). Perceived exertion was significantly greater during P-HIIE compared to S-HIIE at work intervals 1 to 3 (all $P < 0.04$, all ES > 0.58). **Conclusion.** Despite a similar post-enjoyment in both HIIE conditions, S-HIIE could offer superiority to the P-HIIE, which brings significantly greater affective responses for the entire work interval phase, suggesting the viability of this protocol for health strategy promotion in overweight and obese adults.

KEYWORDS: ***Perceptual Responses, Feasibility, Interval Exercise, Overweight, Obesity.***

INTRODUCTION

The prevalence of overweight and obesity has reached global epidemic proportions in adults (1, 2), augmenting concerns about the health problems (e.g., cardiovascular diseases, some cancers, and type 2 diabetes mellitus) associated with this aggravating issue (3). Malaysia is no exception, with current evidence that 1 in 2 adults in Malaysia is overweight or obese (4). A large body of research has revealed that changes in individual lifestyle behaviors, such as regular exercise and a healthy diet, are critical approaches to managing and preventing excess weight in adults (5). Nevertheless, exercise interventions designed to promote long-term effects have been largely unsuccessful due to the greater exercise program attrition among overweight and obese populations (6, 7). Previous studies have shown that an individual's poor exercise adherence and compliance with exercise programs may be attributed to the perceived lack of time, enjoyment, and motivation (7). Consequently, there is a strong rationale to explore alternative

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exercise modalities to improve exercise adherence and potential health benefits in overweight and obese adults.

High-intensity interval exercise (HIIE) is a time-efficient alternative to traditional exercise training, which commonly consists of a higher volume of low to moderate-intensity training (8). It is well established that HIIE elicits comparable or, in some cases, superior improvement in cardiorespiratory fitness and cardiometabolic health than continuous moderate-intensity exercise (CMIE) in overweight and obese adults (9, 10). The application of HIIE as a public health strategy has been disputed, however, mainly because the near-maximal work intensity (e.g., 70% to 100% of maximal effort) performed during HIIE may generate negative affect (feelings of displeasure) and greater exertional stress (11). Evidence has shown that negative affective responses during exercise may lead to poor exercise behavior, intentions, and adherence in adults (12). Despite the requirement of high-intensity effort of HIIE, previous reviews have consistently shown that HIIE generated greater post-enjoyment responses compared to CMIE across populations, including overweight and obese (13, 14). Rhodes and Kates (15) concluded that exercise feelings during exercise had been contributed as a strong predictor of future exercise behavior rather than post-exercise feelings, indicating that enjoyment responses following exercise may not entirely reflect individuals' future exercise motives and behaviors. Therefore, it is crucial to establish both affective and enjoyment responses during HIIE, to gain an overall insight into the implementation and maintenance of interval exercise in overweight and obese populations.

Several studies provided evidence of affective responses to HIIE in overweight and obese adults. For example, Martinez et al. (16) reported that HIIE with short work intervals (30 s and 60 s) elicited greater pleasurable feelings compared to HIIE with longer work intervals (120 s) in overweight and obese adults, which is also in line with a study conducted by Astorino and colleagues (17) in obese women. Despite this valuable information, the work intensity of HIIE was not considered in these studies in overweight and obese adults. Documenting this information is important, given that affective responses during HIIE depend on the intensity of the work interval, but data are currently limited to the prescribed HIIE among non-overweight/obese adults. Available data demonstrate the effect of self-paced HIIE on physiological responses (e.g., HR and exertional stress responses) and exercise performance (e.g., running speed), but the evidence is mainly limited to athlete-based studies and data on affective responses to self-paced HIIE have not been reported (18-20). A review of 31 studies by Ekkekakis (21) concluded that self-paced intensity could facilitate greater positive affective responses (more pleasurable feelings) compared to the prescribed intensity in adults. However, these findings are yet to be explored in HIIE protocol among overweight and obese adults.

Thus, the purpose of the present study was to compare the acute perceptual responses (affective response, perceived exertion, and enjoyment) to prescribed HIIE and self-paced HIIE in overweight and obese adults. It was hypothesized that self-paced HIIE would generate a greater affective (more pleasurable) and enjoyment response accompanied by a lower perceived exertion than prescribed HIIE in overweight and obese adults.

MATERIALS AND METHODS

Participants. Twenty-four overweight and obese adults (8 men and 16 women; range 21-34 years old) volunteered to partake in this study. All participants were overweight-to obese (BMI= 23-30 kg.m^{-2}) based on overweight-to-obese Asian populations classification (1). According to the Physical Activity Readiness Questionnaire, participants were excluded from the study if they had previously been involved in any training program within the past 3 months or had contraindications to exercise. All participants were physically inactive (Category 2, <600 MET-min/week) as assessed by the Malay language version of the International Physical Activity Questionnaire IPAQ-M (22). Written informed consent was acquired from all participants, and the protocol was approved by the Human Research Ethics Committee (USM/JEPeM/19120848). Participants were recruited through E-mail announcements, media socials (e.g., WhatsApp and Facebook), and flyers.

Experimental overview. This study incorporated a repeated measure, within-subjects, parallel-group design, whereby each participant was assigned to two different HIIE conditions: prescribed HIIE (P-HIIE) and self-paced HIIE (S-

HIIE). The randomization between these two groups was stratified by gender (4 men and 8 women for each group). Participants completed two experimental visits in the laboratory, separated by a minimum 2-day rest period. The first visit was to establish participants' anthropometric variables and cardiorespiratory fitness and familiarise participants with the measurement scales. It was followed by completing a running HIIE protocol according to their respective exercise groups (P-HIIE or S-HIIE). All experimental tests were performed at the same time of the day between the hours of 08:00 to 10:00 using a motor-driven treadmill in a sports science laboratory (TMX428CP Trackmaster treadmill, USA). The temperature and humidity of the laboratory were set similarly across conditions (temperatures = 25-26 °C and humidity 55-60%).

Anthropometric and physical activity measures. Body mass and stature were measured to the nearest 0.1 kg and 0.1 cm. Body mass index (BMI) was calculated as body mass (kg) divided by stature (m) squared. Participants' daily habitual physical activity was measured using validated IPAQ-M before the experimental visits (22).

Determination of cardiorespiratory fitness. Participants were habituated to the motorized treadmill before completing an incremental speed-based protocol to establish maximal oxygen uptake ($\dot{V}O_{2max}$) and the ventilatory threshold (VT). Participants began a warm-up at a speed of 4.0 km/h for 3 min, followed by running at the speed of 6.0 km/h with 0.5 km/h increments every 30 s until volitional exhaustion, before a 5 min cool down at 4.0 km/h. Throughout the incremental test, the treadmill gradient was set at 1%. HR was measured continuously using a telemetry system (Polar Electro, Kempele, Finland), and the highest HR achieved during the incremental speed test was taken as HR_{max}. This protocol has been used previously for determining maximal aerobic speed (MAS) in physically active adults (19).

Expired gas exchange and ventilation variables during the cardiorespiratory fitness test were measured using a calibrated metabolic cart (Cortex Metalyzer III B, Leipzig, Germany). HR responses were recorded continuously using a telemetry system (Polar Electro, Kempele, Finland). Both gas exchange and HR data were subsequently averaged over 10-s intervals. The VT was determined from the incremental test data using the ventilatory equivalents for carbon dioxide ($\dot{V}CO_2$) and $\dot{V}O_2$ production. $\dot{V}O_{2max}$ was determined as the highest 10-s average in $\dot{V}O_2$ was elicited either during the incremental or supramaximal test. Both maximal HR (HRmax) and MAS were taken as the highest HR (in bpm) and speed (in km.h^{-1}) achieved during the incremental speed tests, respectively.

HIIE protocols. Participants completed two HIIE conditions consisting of a 3-min warm-up at 4.0 km.h^{-1} followed by 6 x 1-min work intervals performed at either 90% MAS determined from the incremental test (P-HIIE group) or self-paced intensity (S-HIIE group) interspersed with 75 s active recovery. For the S-HIIE group, participants were encouraged to run as fast as they would like for 1 min across six repetitions of the work interval. They were informed there is no right or wrong speed rather selected the speed they felt was their highest effort given the exercise situation. Participants were allowed to adjust their running speed every 10 s before the end of each work interval during S-HIIE. In both P-HIIE and S-HIIE groups, participants dismounted the treadmill during the active recovery periods and were encouraged to pace around the laboratory to avoid any venous pooling and lightheadedness. Heart Rate (HR) was recorded continuously during the HIIE conditions, but no expired gas exchanges (no facemasks) were collected to enhance external validity. A threshold of ≥85 % HR_{max} was used as our criterion for satisfactory compliance with the HIIE protocol (23). The selected interval running protocol was based on a commonly utilized low-volume protocol in HIIE-based studies in adults (24).

Experimental Measures. Affective response (pleasure/displeasure) was measured using the feeling scale (FS; (25)). Participants responded to how they felt on an 11-point bipolar scale ranging from "Very Good" (+5) to "Very Bad" (-5). FS exhibited correlations ranging from 0.41 to 0.59 (with the Affect Grid) (26), indicative of convergent validity with similar established measures (Van Landyut et al., 2000). ΔFS represent the change in the affective response from work interval 1 to the work interval 6 across all HIIE conditions. Participants responded to the FS 5 min before exercise and at 20 s before the end of each work and recovery intervals.

The physical activity enjoyment scale (PACES), which was validated for use with adults (27), was used to assess enjoyment 10 minutes after exercise. The PACES consists of 7 positively and 11 negatively worded items, each rated from 1 to 7 on a 7-point bipolar scale. Negative items were reverse scored, and all 18 items were summed to produce a total enjoyment score out of 126. The present study's internal consistency was acceptable at each administration (Cronbach's αs > 0.90).

Perceived exertion (RPE) rating was assessed using the 10-point category-Ratio 10 Scale (28). Participants were instructed to report perceptions of their exertion via a 0-10-point Likert item ranging from 0 (nothing at all) to 10 (absolute maximum). This scale has been established as a reliable and valid measure of physical exertion during exercise (28). Participants responded to the RPE at 20 s before the end of each work and recovery interval.

Statistical analyses. All statistical analyses were conducted using SPSS (SPSS 26.0; IBM Corporation, Armonk, NY, USA). Descriptive characteristics are presented as mean ± standard deviation (SD). The Shapiro–Wilk normality test checked the normal distribution of the data. The independent t-tests were conducted to explore differences between groups across multiple baseline characteristics and post-enjoyment scores between conditions. A two-way mixed ANOVA was conducted to examine differences in affective and RPE responses in a series of two conditions (P-HIIE vs. S-HIIE; between factor) by 6 (work intervals; within factor). Bonferroni post hoc test was carried out on significant interactions to examine the location of differences. Where the assumption of sphericity was violated, degrees of freedom were corrected with Greenhouse–Geisser epsilon. The magnitude of mean differences was interpreted using effect size (ES) calculated using Cohen's *d* (**29**).

RESULTS

Table 1 summarizes the baseline characteristics of the two HIIE conditions. There were no statistically significant differences across all characteristics (all P>0.05, all ES<0.36). Based on WHO Asian-BMI classifications, the percentage of overweight (BMI = 23-24.9 $kg.m^{-2}$) and obesity (BMI ≥ 25 $kg.m^{2}$) in the present study was 20.8% and 79.2%, respectively. The participants' fitness levels were classified as very poor to poor ($\dot{V}O_{2max}$: Male 27.2 - 43.5 $mL.min^{-1}.kg^{-1}$; Female 21.7 - 33.6 $mL.min^{-1}.kg^{-1}$) according to the cardiorespiratory fitness norms of the American College of Sports Medicine (ACSM, 2018) for individuals aged 20-29. All participants completed the HIIE with no adverse events, regardless of conditions.

Table 1. Baseline characteristics of the participants for P-HIIE and S-HIIE groups (N =24).

	P-HIIE (n=12)	S-HIIE (n=12)	P-value	ES
Age (y)	26.7 ±4.9	26.6 ± 3.7	1.00	0.02
Body mass (kg)	47.7 ± 6.9	47.8 ± 5.2	0.65	0.02
Stature (m)	1.56 ± 0.10	1.55 ± 0.09	0.89	0.11
BMI ($kg.m^{-2}$)	26.5 ± 1.3	27.3 ± 6.1	0.65	0.18
Body fat (%)	21.1 ± 3.9	23.0 ± 8.8	0.77	0.28
$\dot{V}O_{2max}$ ($L.min^{-1}$)	1.75 ± 0.33	1.68 ± 0.28	0.15	0.23
$\dot{V}O_{2max}$ ($mL.min^{-1}.kg^{-1}$)	28.8 ± 7.8	26.4 ± 6.4	0.42	0.24
HR_{max} (bpm)	181 ± 10	178 ± 13	0.18	0.26
VT ($L.min^{-1}$)	0.75 ± 0.13	0.69 ± 0.20	0.38	0.36
VT (%$\dot{V}O_{2\ max}$)	42.9 ± 15.3	41.7 ± 10.6	0.58	0.09
MAS ($km.h^{-1}$)	10.1 ± 2.1	9.5 ± 1.0	0.16	0.36
IPAQ-M (MET-min/week)	518 ± 334	446 ± 331	0.60	0.22

Values are reported as mean ± standard deviation. Abbreviations: BMI, body mass index; MVPA, moderate to vigorous physical activity; $\dot{V}O_{2max}$, maximal oxygen uptake; HR_{max}, maximal heart rate; %$\dot{V}O_{2max}$, percentage of maximal oxygen uptake; VT, ventilatory threshold.

Heart rate responses. The HR data from P-HIIE and S-HIIE conditions are depicted in Figure 1. There was a significant condition by interval interaction for HR (P<0.01). P-HIIE generated greater HR responses at work interval 1 to 3 compared to S-HIIE [P-HIIE = 145 ± 22 bpm – 156 ± 17 bpm (80%-86% HRmax) vs. S-HIIE = 131 ± 13 bpm – 140 ± 12 bpm (76% vs. 81% HRmax); ES= 0.74 – 1.07]. In both conditions, the majority of the participants (more than 9 participants) reached the cut-off points of ≥85% HRmax and typically occurred following work intervals 3 (P-HIIE) and 4 (S-HIIE).

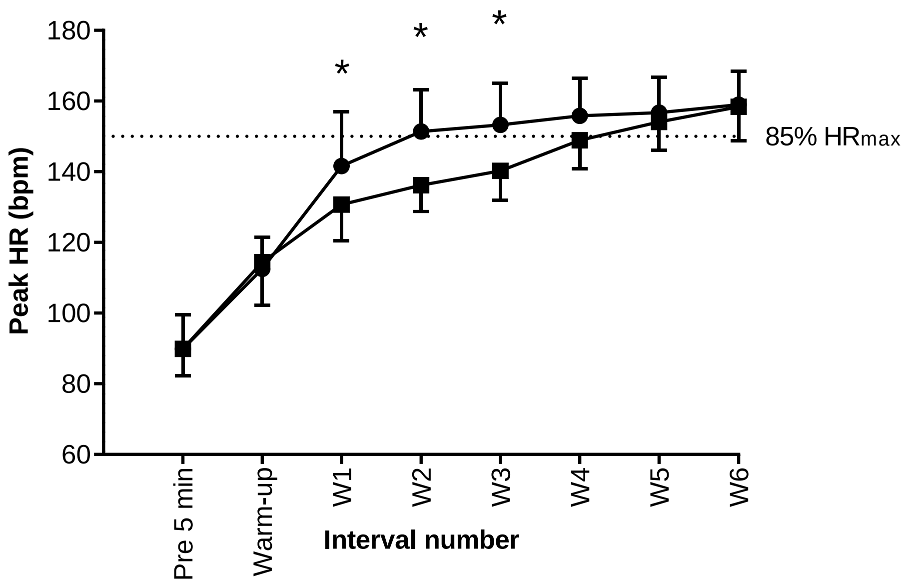

Figure 1. The mean peak HR (in beats per minute) during the work interval phase of the P-HIIE (●) and S-HIIE (■). Where, W=work interval and HR_{max}=maximal heart rate. *Significant difference between groups (P<0.05). Error bars represent the SD values.

Running Speed. Changes in running speed ($km.h^{-1}$) during P-HIIE and S-HIIE are shown in Figure 2. There was a significant condition by interval number interaction for the running speed (P<0.01). P-HIIE generated greater running speed at work interval 1 to 4 compared to S-HIIE [all P<0.23, P-HIIE = 8.8 ± 1.8 $km.h^{-1}$ (90% MAS) vs. S-HIIE = 5.5 ± 0.8 $km.h^{-1}$ to 7.2 ± 1.2 $km.h^{-1}$ (62% MAS to 80% MAS), all ES> 0.98]. Also, there was a significant main effect of interval number for the running speed in S-HIIE (P<0.01). Specifically, running speed increased from work interval 1 to work interval 6 during S-HIIE (all P<0.009, 5.5 ± 0.8 $km.h^{-1}$ to 8.2 ± 1.8 $km.h^{-1}$, 62% MAS to 90% MAS, all ES>0.75). Also, there was a strong positive correlation between running speed and HR responses for S-HIIE across work intervals (P<0.01; r>0.91).

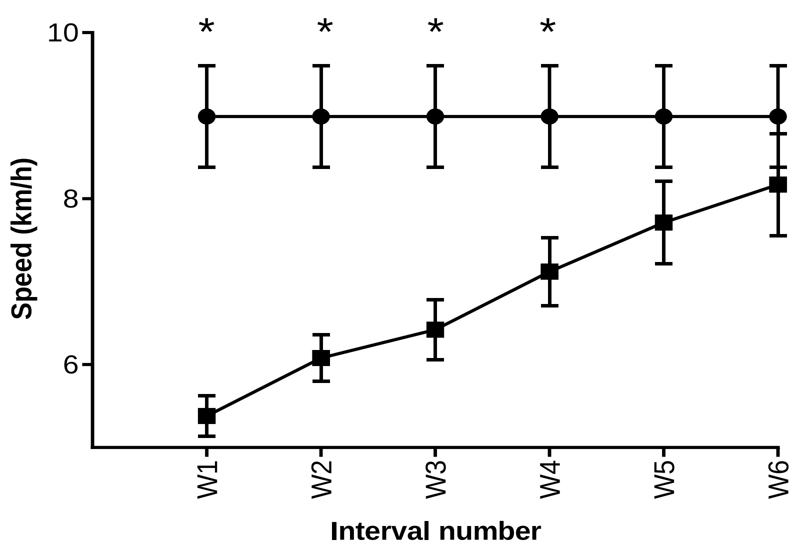

Figure 2. Running speed in kilometers per hour during the interval phase of the P-HIIE (●) and S-HIIE (■). Where, W = work interval. *Significant difference between groups (P<0.05). Error bars represent the SD values.

Affective responses. Changes in affective responses measured by FS in both HIIE conditions are illustrated in Figure 2. There was a significant condition by interval interaction for FS ($P<0.05$). P-HIIE elicited lower FS across all work intervals than S-HIIE (all $P<0.03$, all $ES>0.66$). ΔFS was significantly greater in P-HIIE than in S-HIIE ($P<0.05$, -1.8 ± 0.9 vs. -1.0 ± 1.2, ES=0.75). FS remained positive at work interval 6 during P-HIIE (1.0 ± 0.8 on FS score) in 11 participants (92%) and in all participants (100%) during S-HIIE (2.58 ± 1.5 on FS score).

RPE and enjoyment responses. RPE responses during both HIIE conditions are illustrated in Figure 3. RPE showed a significant condition by interval number interaction ($P<0.05$). RPE was significantly greater during P-HIIE than S-HIIE at work-intervals 1 to 3 (all $P<0.04$; P-HIIE= 2.7 ± 0.5 to 4.2 ± 0.6 vs. 2.0 ± 0.8 to 3.7 ± 0.9; all $ES > 0.58$).

Enjoyment responses (Figure 3) measured via post-exercise PACES scores showed no significant difference between the two HIIE conditions ($P=0.42$, ES=0.40). Specifically, the P-HIIE group averaged 117 ± 7, whereas the S-HIIE group averaged 120 ± 8, on a scale on which 72 is the midpoint and 126 represents maximum enjoyment responses.

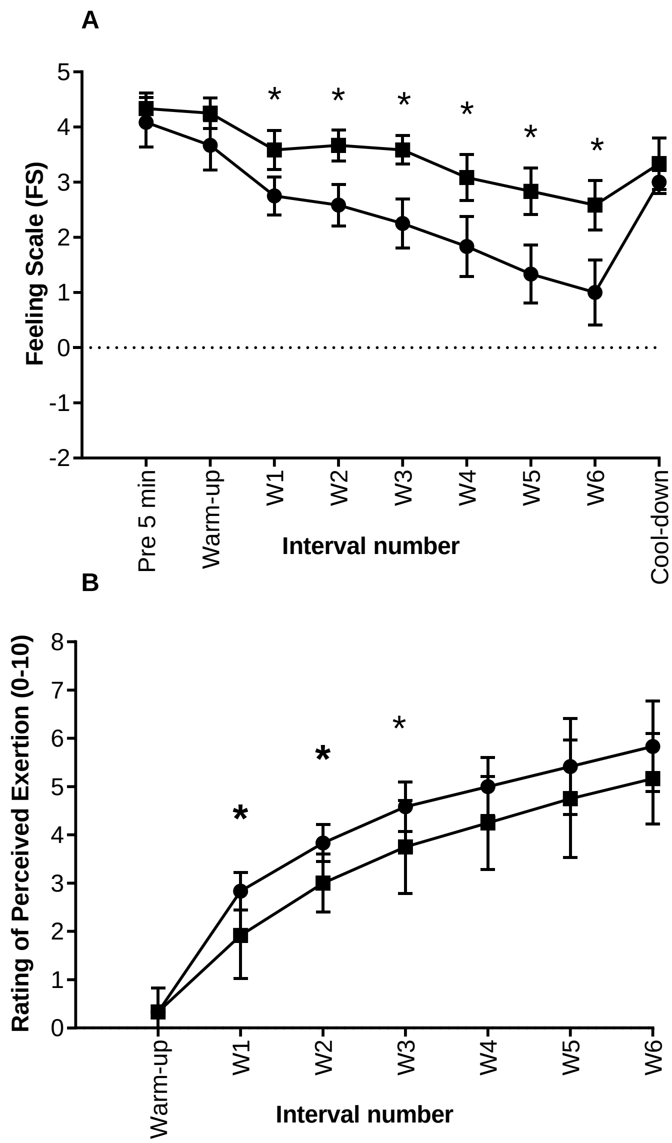

Figure 3. Feeling scale (A) and rating of perceived exertion (B) during the interval phases of the P-HIIE (●) and S-HIIE (■). Where, W = work interval. *Significant difference between groups ($P<0.05$). Error bars represent the SD values.

DISCUSSION

The current study depicts data on the affective, perceived exertion, and enjoyment responses during HIIE with different work intensity conditions, namely, prescribed HIIE (P-HIIE) and self-paced HIIE (S-HIIE) in overweight and obese adults. The primary research question focused on which condition would be considered the most viable protocol (i.e., pleasurable, enjoyment, less exertional effort) for overweight and obese individuals. The key findings from this study are: 1) the S-HIIE group elicited lower running speed during the initials work intervals compared to P-HIIE, 2) the P-HIIE group elicited lower positive affective responses (less pleasurable) across all work intervals compared to S-HIIE, 3) P-HIIE generated greater perceived exertion during the first three work intervals than S-HIIE, and 4) similar post-enjoyment was observed for both HIIE conditions.

In the present study, we found an increase in running speed across S-HIIE work intervals (~ 62% to 90% of MAS), which is consistent with the recent HIIE study in moderately active adults conducted by Mohd-Liza and colleagues (30). The author has reported that when given a chance to self-regulate work intensity during treadmill interval running, participants tend to initially regulate a lower running speed, followed by a greater running speed towards the end of exercise (~ 52% to 90% of MAS). Our data strengthen this valuable finding related to the self-paced treadmill interval running prescriptions for the overweight and obese cohort. The teleoanticipation model proposed that the subconscious brain controls physical effort during self-paced exercise to allow an individual to exercise without overly stressing the physiological responses (e.g., HR responses). The present study further supports this notion via the positive correlation between running speed and HR responses during S-HIIE. Our data reinforced that the individual's physiological stress, as reflected in HR, may control the degree of physical effort (i.e., running speed) a person is willing to exert during S-HIIE.

Consistent with the study hypotheses, affective responses measured by FS scores during S-HIIE generated greater affective responses (more pleasurable) across all work intervals compared to P-HIIE. Substantial evidence has been provided to indicate that affective response to self-paced exercise seems more positive than imposed intensity exercise in adults (21). However, the available data are limited to continuous exercise rather than interval exercise. Previous HIIE-based studies have reported that affective responses during HIIE depend on the intensity of the work interval (i.e., running speed or peak power output) (14, 31). Therefore, it appears that the pacing strategies (i.e., regulation of running speed) adopted by our participants may be attributed to the greater pleasurable feelings for the entire work intervals during S-HIIE compared to P-HIIE in overweight and obese adults.

Previous studies also have shown that participants' choice over their behavior leads to greater perceptions of competence and feelings of autonomy, enhancing individuals' affective responses. This viewpoint is posited by a self-determination theory (32) framework, which suggests that the degree of pleasure that an individual experiences when they act autonomously is probable to be greater than that experienced when behavior is externally controlled. Our data reinforced this notion by showing that 'choice' and 'control' over the work intensity perceived by the participants during S-HIIE contributed to greater positive affective responses than externally controlled work intensity during P-HIIE. Nevertheless, similar post-enjoyment was observed in both P-HIIE and S-HIIE conditions. According to the attribution theory (33), individuals may attribute perceived competence and success based on their greater effort or challenge toward a specific task, and this achievement-related behavior is linked to enjoyment levels. Therefore, the reason that comparable challenges posed during P-HIIE and S-HIIE, as indicated by the similar running speed and perceived exertion responses towards the end of exercise completion (see Figure 3), are likely to account for the similar post-enjoyment responses in both HIIE conditions.

Although evidence on health-related outcomes is not available in this present study, previous studies have proposed using a cut-off point of ≥85% HRmax to serve as an indicator for the facilitation of multiple health benefits, including improvement in cardiometabolic risk profile and cardiorespiratory fitness in adult (9, 24). The cut-off points of ≥85% HRmax were attained following the third and fourth work intervals in P-HIIE and S-HIIE, respectively, and HR responses drifted upward until HR reached 89–91% HR_{max}

at the end of the work interval in both conditions. Although evidence on cardiorespiratory responses during HIIE in overweight and obese is limited, our study's pattern of HR responses is in line with previous HIIE-based studies in this cohort. For example, Smith-Ryan (34) observed that HR responses were typically lower (< 85% HR_{max}) following the first three work intervals when compared to the overall work interval phases in the prescribed HIIE protocol of a 10 x 1-minute conducted in overweight and obese adults. Our finding extends previous work involving HIIE protocol in overweight and obese adults by showing that self-paced HIIE could offer comparable HR response patterns to prescribed HIIE protocols.

The present study is limited to exercise conducted in a laboratory, which is unlikely to reflect a participant's real-world affective response to exercise. However, a laboratory setting (with limited social, auditory, and visual interaction) was adopted in the present study to ensure an accurate comparison of perceptual responses (i.e., affect, enjoyment and RPE) across all exercise conditions. Another limitation is that this study examined the acute effect of perceptual responses to HIIE rather than the long-term effect. Therefore, future studies should consider investigating similar HIIE protocols as in the present study but in outdoor-based settings across several weeks of exercise intervention (e.g., 2 to 10 weeks) with the comparisons between overweight and obese adults.

CONCLUSION

Our data extend the previous HIIE-based studies in overweight and obese adults and indicate that self-paced HIIE (S-HIIE) offers advancement to the prescribed HIIE (P-HIIE), which brings significant greater affective responses (more pleasurable) across all work intervals. Although data on the relationship between affective responses and long-term behavioral maintenance of exercise are not available in this study, it is plausible to suggest that performing S-HIIE protocols could promote better exercise adherence and implementation, considering the greater affective responses when promoting such behavior in overweight and obese adults. Therefore, when incorporated with the HR responses data, our evidence indicates that S-HIIE could potentially serve as a suitable alternative to P-HIIE prescription to promote health in overweight and obese adults.

APPLICABLE REMARKS

- S-HIIE elicited greater affective responses for the entire work interval phases than P-HIIE.
- Similar enjoyment responses were evident following P-HIIE and S-HIIE.
- S-HIIE generated comparable heart rate responses pattern as in P-HIIE.

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AUTHORS' CONTRIBUTIONS

ALA, AAM, HAH, and ASM conceived the idea for the study; AAM, HAH, and ASM obtained funding for the study; AM and HAH designed the trial protocol; ALA recruited participants and coordinated the trial; ALA and AAM were responsible for statistical analyses; ALA and AAM drafted the manuscript, and all authors read and approved the final version for submission.

CONFLICT OF INTEREST

No conflict of interest to declare.

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