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Going High to Keep Body Mass Low: How Post-Exercise Exposure to a Simulated High Altitude Influences Energy Balance—A Proof-of-Concept Pilot Study

Peyton E. Allen, Akinola D. Akinwumi, Evan G. Kroeze, Paula Y. Leigh, Sahnet N. Ramirez, Gregory L. Smart, Tay M. Thomas and Hunter L. Paris *

Department of Sports Medicine, Pepperdine University, Malibu, CA 90263, USA
* Correspondence: hunter.paris@pepperdine.edu

Abstract: A healthy body mass contributes to a positive quality of life, and for overweight/obese individuals, weight loss of even modest proportions improves health-related outcomes. A novel approach to promoting body mass regulation is to pair exercise with high altitude, thereby upregulating metabolic processes and increasing caloric expenditure. As an added measure of body mass regulation, data suggest that high altitude stimulates the production of the appetite-suppressing hormone leptin. Issues arise, however, given that high altitude compromises aerobic exercise capacity. Whereas exercising at high altitude may compromise exercise intensity and duration, *recovering* at high altitude retains the integrity of exercise while still potentially conferring the benefits of the low oxygen environment on energy expenditure and energy intake. The purpose of this study was to perform a proof-of-concept pilot test on whether post-exercise exposure to a simulated high altitude influenced acute energy balance. Twelve healthy men and women ran for 30 min at a moderate intensity on two separate occasions. Following exercise, participants recovered for 30 min while breathing either sea level air or low oxygen air simulating high altitude (equivalent to 4500 m elevation). Blood samples and hunger ratings were collected pre-exercise and post-recovery. Heart rate was recorded throughout exercise and recovery and used to calculate caloric expenditure. Post-exercise energy expenditure was significantly higher (p = 0.03) following high altitude recovery (139 ± 15 kcal) compared to sea-level recovery (98 ± 11 kcal). Participants reported a lower desire to eat when they recovered in the high altitude environment (p = 0.01), though post-recovery leptin concentrations were similar between the two conditions. Post-exercise exposure to a simulated high altitude environment represents a promising method for increasing daily caloric expenditure and lowering appetite. Given the pilot nature of this study, future research is needed to address the question of high altitude recovery on a larger sample over a longer time period and with robust measures of caloric expenditure.

Keywords: obesity; hypoxic conditioning; body mass regulation; weight loss

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1. Introduction

One billion people are expected to have obesity by the year 2030, including one in five women and one in seven men [1,2]. Efforts to circumvent this projection estimate that if total daily energy expenditure increased by as little as 50–100 kcals per day, weight gain could be prevented in 90% of adults [3]. Perhaps the most reliable method of elevating energy expenditure—and the intervention that consistently garners favorable cardiometabolic benefits—is exercise. Maintaining a healthy body mass requires more than a systematic increase in energy expenditure, however, and keeping in mind the dual-sided nature of energy balance, any increase in energy expenditure could be countered by a compensatory elevation in energy intake. Here again, exercise proves beneficial as it both elevates caloric expenditure and appropriately regulates appetite [4,5]. But despite the known benefits

of physical activity, long-term adherence to exercise routines is infamously poor [6,7]. As such, strategies other than exercise have been sought to encourage a healthy body mass, including ingestion of thermogenic substances [8,9], supplementation with pharmacological interventions [10,11], and alteration of environmental conditions [12].

Amongst the potential environmental therapeutics that have been considered for weight maintenance, exposure to high altitude has been shown to elevate energy expenditure (perhaps via the stimulation of the sympathetic nervous system [13–15]), lower energy intake (potentially via alterations in appetite hormones such as leptin [16]), and improve blood glucose regulation as well as markers of inflammation [17]. Given the capacity for high altitude to influence both sides of the energy balance equation and the ability for exercise to do likewise, a possible synergistic relationship between exercise and high altitude exists. This theory posits that exercising in a highland setting confers a more robust influence on body mass compared to exercising at sea level [18–20]. While this idea holds theoretical promise, exercising in high altitude presents difficulty in application. One hurdle to overcome is that traveling to highland settings is not feasible for everyone. To address this, research has employed a simulated high altitude, i.e., normobaric hypoxia. This is achieved by reducing the inspired O_2 fraction (FiO_2), thereby permitting people to live near sea level and yet achieve periodic episodes of hypoxic exposure. Another obstacle is the strenuous nature of exercising at high altitude. If an absolute exercise intensity is maintained between sea level and hypoxia, the perceived exertion increases in hypoxia, and exercise duration diminishes [21,22]. By compromising exercise duration, the addition of hypoxia might weaken the very exercise-induced adaptations it sought to support.

Although exercising in hypoxia may therefore work against body mass regulation, the influence of exercise on caloric expenditure extends beyond the exercise bout itself, as metabolic processes remain elevated during the post-exercise recovery. While the relationship between aerobic exercise and hypoxia may be antagonistic (with hypoxia shortening exercise duration), this same relationship may be complementary during the post-exercise recovery period if hypoxia prolongs the return to homeostatic baseline. By preserving the magnitude of effect elicited during sea level exercise and permitting the added benefits of exposure to a simulated high altitude, exercising in normoxia but recovering in hypoxia may evoke a metabolic response that promotes weight maintenance. Although a comprehensive understanding for the physiological ramifications of hypoxia during recovery is lacking, prior investigations indicate that hypoxic recovery may weaken mitochondrial adaptations to exercise [23] and compromise cerebral oxygenation [24]. Conversely, recovering from exercise in a hypoxic environment may promote iron absorption [25] and blunt oxidative stress [26]. The influence of hypoxic recovery on body mass regulation remains largely unknown. The purpose of this proof-of-concept pilot study was to test whether recovering from exercise at a simulated high altitude influences energy expenditure and energy intake. We hypothesized that recovering from exercise at a simulated high altitude amplifies post-exercise energy expenditure compared to sea level recovery, while simultaneously suppressing appetite [27,28]. In line with previous experimental data demonstrating variability in the physiological responses to hypoxia [29,30], we examined whether variant responses in energy expenditure and energy intake might be related to sex differences or to the magnitude of arterial oxygen desaturation.

2. Materials and Methods

2.1. Participants

Participant characteristics are provided in Table 1. Twelve active individuals (6 men, 6 women) volunteered to participate in the study. Women were tested during the early follicular phase of the menstrual cycle, within 10 d of the onset of menses according to self-report. All participants were healthy as indicated by the Physical Activity Readiness Questionnaire (PAR-Q+). Participants were excluded if they had a current or recent ($\leq$2 mo) injury or obtained a $\dot{V}O_2$peak < 40 mL·kg^{-1}·min^{-1} for women and <45 mL·kg^{-1}·min^{-1} for men. Upon arrival at the laboratory participants completed a 7 d training log and a

24 h dietary recall and were instructed to repeat similar diet and activity patterns before subsequent visits. Participants were tested at the same time of day at each of the experimental visits (Visits 2 and 3) and were instructed to arrive at the laboratory on a 2 h fast, having abstained from strenuous exercise for the previous 24 h. All protocols and informed consent were approved by the Pepperdine University Institutional Review Board.

Table 1. Participant characteristics.

Variable	Mean	±	SE
Age (y)	23	±	2
Body mass women (kg)	61.6	±	1.4
Body mass men (kg)	71.0	±	4.8
Height women (cm)	169.5	±	2.2
Height men (cm)	180.2	±	3.3
$\dot{V}O_2$peak ($L \cdot min^{-1}$)	3.3	±	0.2
$\dot{V}O_2$peak women ($mL \cdot kg^{-1} \cdot min^{-1}$)	45.4	±	1.5
$\dot{V}O_2$peak men ($mL \cdot kg^{-1} \cdot min^{-1}$)	52.7	±	2.7
$\dot{V}_{Emax}$ women ($L \cdot min^{-1}$)	102.4	±	5.2
$\dot{V}_{Emax}$ men ($L \cdot min^{-1}$)	144.1	±	7.0

n = 12 participants (6 men, 6 women). $\dot{V}O_2$peak, peak oxygen consumption; $\dot{V}_{Emax,}$ maximum minute ventilation.

2.2. Study Design

A single-blind, randomized, crossover design was implemented where participants completed 3 visits to the laboratory. All exercise occurred on a motorized treadmill (Trackmaster TMX 3030C, Full Vision Inc., Newton, KS, USA). Visit 1 consisted of an incremental running test to exhaustion to determine $\dot{V}O_2$peak. For Visits 2 and 3 participants ran on a treadmill for 30 min at a moderately hard intensity while breathing normal room air (normoxia), followed immediately by 30 min of recovery while breathing either normoxic air or air simulating a high altitude (hypoxia). Air inspired during the hypoxic recovery contained 12% O_2 (equivalent to 4500 m elevation). During Visits 2 and 3, blood was drawn from an antecubital vein before exercise and following 30-min of recovery to test for the anorexigenic hormone leptin. The study design is displayed in Figure 1.

Visit 1: $\dot{V}O_2$peak test. Visit 1 included a running test to exhaustion for determination of $\dot{V}O_2$peak. Treadmill speed began at 10 $km \cdot h^{-1}$ and increased speed 1 $km \cdot h^{-1}$ every 2 min until volitional exhaustion [31]. Following completion of running exercise, participants were familiarized with all testing procedures.

Visits 2–3: 30 min run and 30 min recovery. During Visits 2 and 3, participants ran for 30 min on a treadmill at a moderately hard intensity (70–85% $\dot{V}O_2$peak) and then recovered from exercise for 30 min while breathing either normoxic or hypoxic air. The condition (normoxic recovery or hypoxic recovery) was randomized to avoid an order effect. Visits 2 and 3 were separated by a minimum of 48 h.

Ratings of perceived hunger and satiety were taken at three time points: pre-exercise, immediately post-exercise, and following 30 min of recovery, using a 100 mm visual analog scale questionnaire as used in our laboratory previously and as described elsewhere [32]. Blood samples were obtained at similar time points. Upon completion of questionnaires and preliminary blood measurements, participants' resting data were collected for 5 min before then completing 30 min of running exercise. Minutes 0–2 of running were performed at 60% of $\dot{V}O_2$peak. Treadmill speed was then increased to 70% of $\dot{V}O_2$peak for minutes 2–25. During the last 5 min of the 30 min run, treadmill speed was increased to a pace eliciting 85% of $\dot{V}O_2$peak. Rating of perceived exertion (RPE; Borg original 6–20 scale) [33] was obtained every 5 min during running exercise. Minute ventilation ($\dot{V}_E$), $\dot{V}O_2$, RER, and HR were recorded throughout exercise.

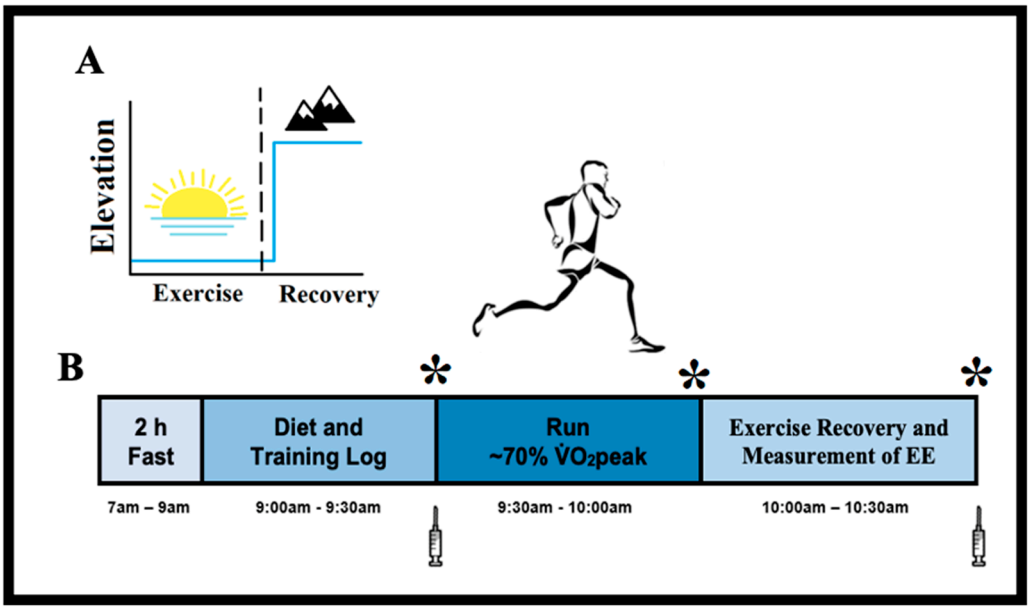


Figure 1. Schematic representation of the experimental design. Study design depicting exercise at sea level and recovery at a simulated high altitude. (**A**) Visits 2 and 3 required running exercise at sea level followed by a 30 min recovery where participants breathed normal room air or hypoxic air simulating high altitude (**B**). Symbol of hypodermic needle represents venous blood draw; star represents time points for measuring hunger/satiety and lactate via finger stick. $\dot{V}O_2$peak, peak oxygen consumption. Indicated times (e.g., 7 a.m.–9 a.m.) are examples only as participants arrived at various times throughout the morning hours. Inspired gas during measurement of energy expenditure (EE) represents the lone difference between Visits 2 and 3.

Immediately following exercise cessation, participants were connected (via corrugated tubing on the inspiration side of an oronasal facemask) to a reservoir of air containing either normoxic or hypoxic air. Participants laid supine for 30 min, recovering from exercise while breathing from the given reservoir. Heart rate was monitored throughout recovery and arterial O_2 saturation (SpO_2) was estimated using a pulse oximeter (OxiMax N-600×; Nellcor, Minneapolis, MN, USA). Following 30 min of recovery, perceived hunger and satiety were recorded and blood measurements were again performed.

2.3. Metabolic Responses to Exercise

Metabolic and ventilatory variables were continuously measured during exercise in Visits 1–3. Participants wore an oronasal face mask (7450, Hans Rudolph, Shawnee, KS, USA) and breathed through a two-way nonrebreathing valve (2700, Hans Rudolph) connected to a flow sensor and portable gas analysis system (K5, COSMED, Concord, CA, US) displaying breath-by-breath $\dot{V}O_2$ and $\dot{V}_E$. Gas analyzers were calibrated prior to each visit with known gas concentrations within the physiological range. Heart rate (HR) was obtained continuously during exercise and recovery with a telemetry transmitter (GARMIN, Olathe, KS, USA) and time-averaged every 5 min. Energy expenditure during the post-exercise recovery period was estimated from HR using a mixed model analysis that accounts for age, sex, body mass, and $\dot{V}O_2$peak and which has previously been shown to estimate energy expenditure with a high degree of accuracy [34].

2.4. Hypoxic Delivery System

A 1000 L balloon reservoir was connected via corrugated tubing to the inspired breathing port of the oronasal mask worn by participants. Prior to participant arrival, the balloon was filled to capacity with 12% O_2 and balance N_2 using a nitrogen generator (CAT 12, Colorado Altitude Training, Boulder, CO, USA). The balloon was filled during both

normoxic and hypoxic test days to blind participants to the inspirate. During normoxia, a valve to the balloon stayed closed, while a valve to room air remained open so that participants breathed only room air. An O_2 analyzer (S-3A; Ametek Thermox Instruments, Pittsburgh, PA, USA) was used to confirm the fraction of inspired O_2 (FiO_2).

2.5. Blood Measurements

Pre-exercise and immediately following the 30 min recovery, 5 mL of blood was collected in EDTA-coated tubes for the analysis of plasma leptin. Samples were centrifuged at 1300× *g* and 4 °C for 10 min (Sorvall ST8R; Thermo Fisher Scientific, MA, USA). After centrifugation, the supernatant was pipetted from the blood collection tube, transferred to microfuge tubes for storage at −80 °C, and later measured in duplicate for leptin. Leptin was determined with a colorimetric assay [lower limit of detection: 2 pg·mL^{-1}; intra-assay precision: coefficient of variation (CV), 10%; inter-assay precision: CV < 12%] per the manufacturer's protocol (RayBiotech, Norcross, GA, USA). The assay produced a yellow hue and absorption was read at 450 nm.

Blood lactate was measured at three time points: prior to warming up, 4 min after the end of the 30 min run according to post-exercise lactate kinetics [35], and immediately following the 30 min recovery. A fingertip blood sample was taken and analyzed for lactate concentration using a portable lactate analyzer (Lactate Pro 2, ARKRAY Inc., Kyoto, Japan). Altogether, two venous samples and three fingertip lactate samples were taken during each experimental visit (Figure 1).

2.6. Statistical Analysis

A sample size of n = 6 was determined based on a power analysis (G*Power 3.1; Germany) that would allow detection of significant differences in energy expenditure [36] and leptin [37] with statistical power of $1 - \beta = 0.80$ and $\alpha = 0.05$. Statistical analyses were performed with SigmaPlot version 14.0 (Systat Software, San Jose, CA, USA). Data were assessed for normality using a Shapiro–Wilk test. Sphericity of data was assessed using Mauchly's test. For single variables examined between conditions only (e.g., energy expenditure), data were analyzed using paired *t*-tests, and for variables measured at multiple time points during exercise or recovery (e.g., $\dot{V}O_2$ during exercise), a two-way repeated measures ANOVA (experimental condition × time) was used. Bonferroni-corrected post-hoc tests were applied to identify differences. Statistical significance was set at $p < 0.05$. Data are presented as means ± SE.

3. Results

Testing was well tolerated by all participants, with no feelings of sickness or excess discomfort reported during the hypoxic recovery period. Following completion of the study, participants were unable to identify which visit was under hypoxia.

3.1. Energy Expenditure

Heart rate data (Figure 2A) were used to estimate energy expenditure during the 30 min recovery period. Recovering for 30 min in hypoxia significantly increased post-exercise energy expenditure (139 ± 15 kcal) compared to recovering in normoxia (98 ± 11 kcal; $p = 0.03$); the hypoxic environment increased post-exercise energy expenditure in every participant. The magnitude of increase was 42 ± 9 kcals, reflecting a mean increase in 30 min energy expenditure of ~10% when recovering in hypoxia compared to normoxia. Individual energy expenditure and group means are displayed in Figure 2B.

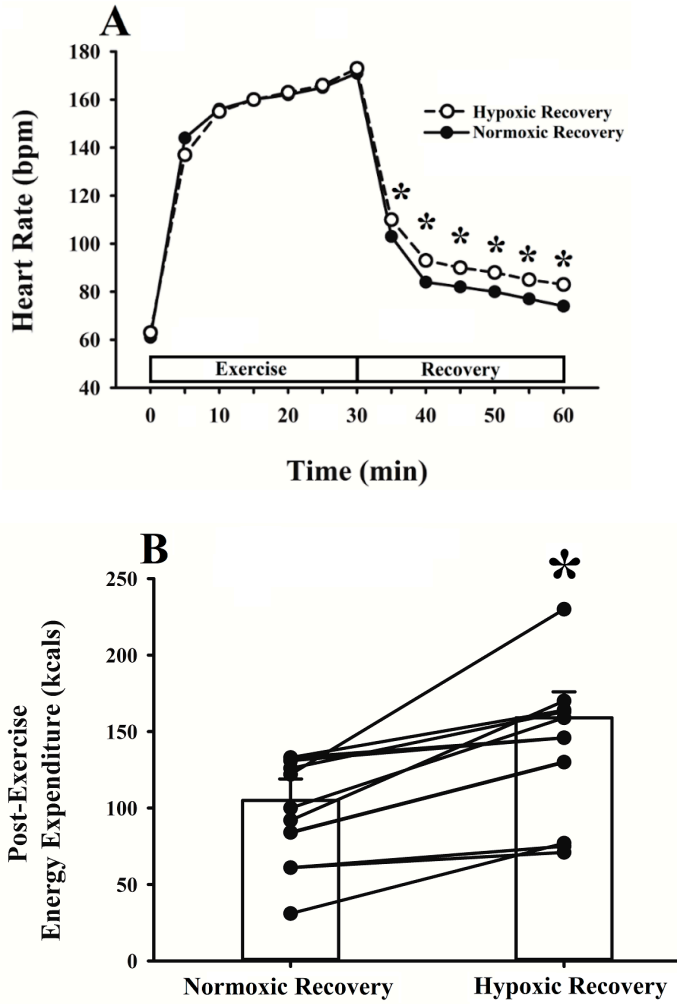


Figure 2. Influence of hypoxic recovery on energy expenditure. Heart rate response to exercise at sea level and recovery in either hypoxia or normoxia. Values are presented as means without standard error bars to increase clarity. * $p < 0.05$ compared to normoxic recovery at same time point (**A**). Group (bars) and individual (lines) data demonstrating post-exercise energy expenditure in response to either hypoxic recovery or normoxic recovery following exercise at sea level. Data are mean ± SE. * $p < 0.05$ (**B**).

3.2. Energy Intake

To further explore the influence of high altitude recovery on energy balance, we quantified changes in hunger and satiety by measuring the anorexigenic hormone leptin. Baseline leptin concentrations were similar between conditions ($p = 0.18$), and thirty minutes of running exercise followed by thirty minutes of recovery did not influence circulating leptin in either condition. (Figure 3A). To supplement these objective measures, we also collected subjective measures of hunger and satiety pre-exercise, post-exercise, and following 30 min of recovery. Although no differences were observed in leptin concentrations, participants reported a lower desire to eat ($p = 0.01$) and a reduced degree of hunger ($p = 0.009$) when recovering in the simulated high altitude environment (Figure 3B,C).

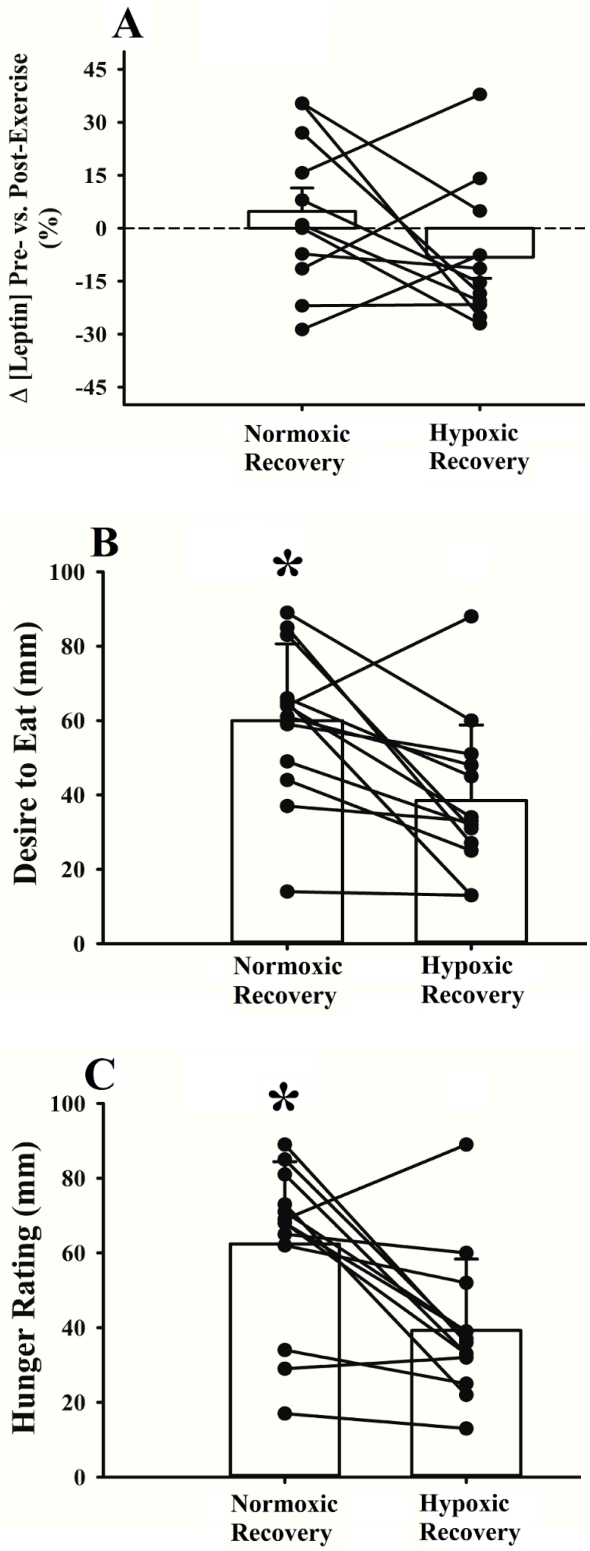


Figure 3. Appetite following 30 min of exercise at sea level plus 30 min of recovery at sea level or at simulated high altitude. Leptin response to exercise at sea level and recovery at sea level or at simulated high altitude (**A**). Ratings of perceived hunger based on the question "How strong is your desire to eat right now?". (**B**). Ratings of perceived hunger based on the question "How hungry do you feel right now?". (**C**). Bars represent condition means and lines denote individual participant responses. Data are mean ± SE. * $p < 0.05$ compared to hypoxic recovery.

3.3. Metabolic and Ventilatory Responses

The metabolic and ventilatory responses to exercise were similar between conditions. Average running velocity during the 30 min exercise was ~12 km·h^{-1} (roughly 8 min·mile^{-1}). Table 2 displays the average HR, $\dot{V}_E$, $\dot{V}O_2$, and RPE during running exercise. Pre-exercise lactate concentrations were similar between conditions (p = 0.41). By study design, sea level exercise increased lactate concentrations to comparable levels in the normoxic (6.5 ± 1.0 mmol·L^{-1}) and hypoxic (6.3 ± 1.0 mmol·L^{-1}) conditions (p = 0.64). Recovering for 30 min in hypoxia did not influence the post-exercise return of blood lactate (3.5 ± 0.5 mmol·L^{-1}) compared to recovering at sea level (3.4 ± 0.4 mmol·L^{-1}; p = 0.70).

Table 2. Metabolic and ventilatory responses during 30 min of running exercise.

	HR (bpm)	$\dot{V}_E$ (L·min^{-1})	$\dot{V}O_2$ (mL·kg^{-1}·min^{-1})	RPE
Normoxic Recovery	167 ± 5	82.2 ± 3.8	42.7 ± 1.5	14 ± 1
Hypoxic Recovery	164 ± 4	82.1 ± 4.6	42.5 ± 1.8	13 ± 1

Data are averages over 30 min of exercise duration ± SE. HR, heart rate; $\dot{V}_E$, minute ventilation; $\dot{V}O_2$, oxygen consumption; RPE, rate of perceived exertion on a scale from 6 to 20. No statistical differences were observed between groups during exercise.

3.4. Group-Specific Responses to Post-Exercise Hypoxia

To investigate possible disparate group responses, we stratified energy expenditure according to whether SaO_2 was defended in hypoxia, and according to sex. Average SaO_2 during the post-exercise period was 97 ± 0.3% in normoxia and 81 ± 1% in hypoxia (p < 0.001). Despite each participant inspiring 12% O_2 during recovery in the hypoxic condition, SaO_2 demonstrated wide variability between participants (71–91%). Those who averaged an SaO_2 ≥ 80% experienced an increase of 57 ± 13 kcals in the hypoxic setting while those who maintained an SaO_2 < 80% experienced an increase of 23 ± 7 kcals (p = 0.06; Figure 4A). When examined according to sex, women burned 28 ± 6 kcals more in the hypoxic setting compared to the normoxic setting, whereas men saw an increase of 53 ± 15 kcals (p = 0.21 compared to women; Figure 4C). Neither sex (Figure 4D) nor the SaO_2-response to hypoxia (Figure 4B) influenced the hunger rating following hypoxic recovery (p = 0.59 and p = 0.96, respectively).

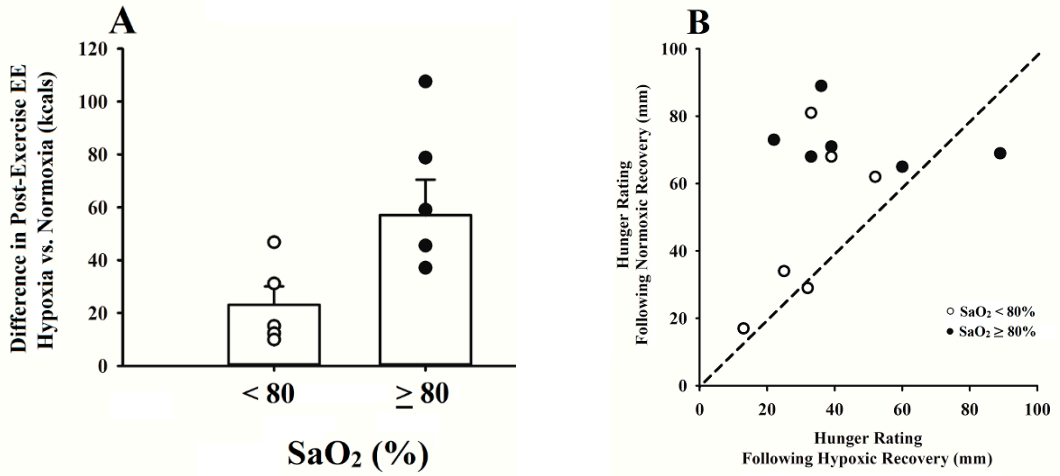


Figure 4. *Cont.*

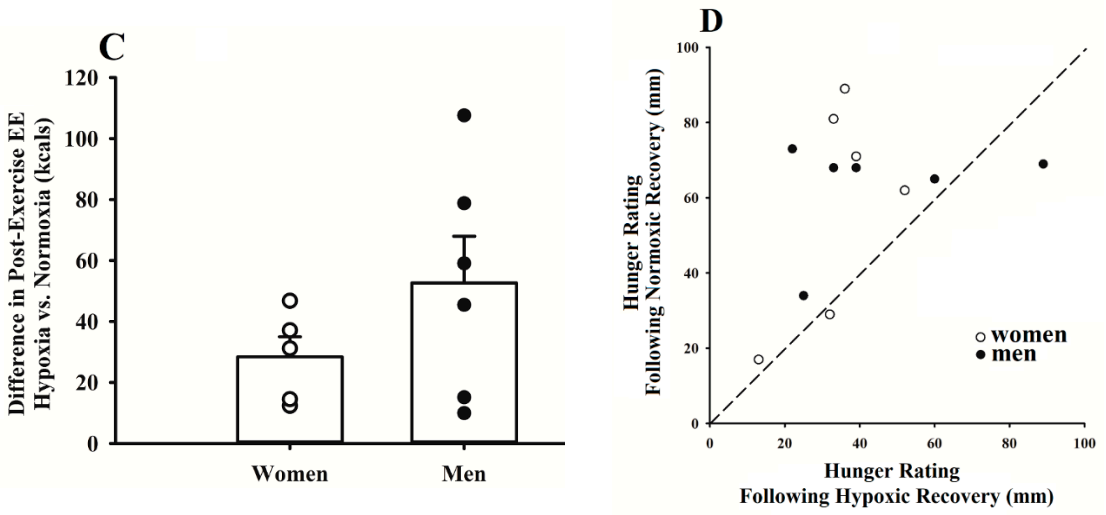


Figure 4. How sex and the degree of oxygen desaturation influence energy balance. Energy expenditure (**A**) and hunger rating (**B**) based on whether SaO_2 was maintained above or below 80% during hypoxic recovery. Differences in energy expenditure (**C**) and hunger rating (**D**) between women and men. No statistical differences were observed either between men and women or between those who defended oxygen saturation above 80% and those who desaturated to a greater degree. EE, energy expenditure. SaO_2, arterial oxygen saturation measured via pulse oximeter.

4. Discussion

Assuming no change in dietary intake or alternative compensatory response, an increase in total daily energy expenditure of 50–100 kcals has been proposed as sufficient to prevent weight gain [3,38]. The purpose of our proof-of-concept pilot study was to determine if altering the environmental conditions in which a person recovers from exercise might contribute towards this increase in caloric expenditure. We report that 30 min of post-exercise hypoxic exposure promotes additional caloric expenditure for a given bout of exercise while simultaneously reducing hunger. Simulated high altitude recovery had a universal effect on energy balance, as differing group-specific responses based on sex and SaO_2 at high altitude were not observed.

4.1. Energy Expenditure

When sea level exercise was concluded with 30 min of recovery in a simulated high altitude, post-exercise energy expenditure was elevated by an average 42 $\pm$ 9 kcals, thereby approaching—though falling short of—the mark set by Hill and colleagues as the threshold required to halt weight gain [3,38]. Although our study design did not permit detailed insights into the mechanism behind this increase in caloric expenditure, previous research and observational data provide evidence that elevations in altitude correlate with elevations in catecholamine release [22,39]. Considering these findings, our study hypothesized that sympathetic stimulation by hypoxia would work in concert with the sympathetic signal still lingering from a bout of exercise to confer a more robust energy expenditure when exercise recovery occurred in hypoxia. Consistent with Moore et al.'s [40] findings that acute hypoxic exposure is sufficient to incite sympathetic activation, heart rate remained elevated during 30 min of hypoxic recovery, while returning more quickly to resting values during normoxic recovery—thereby suggesting a prolonged period of elevated sympathetic activity as a contributor to the observed elevated energy expenditure. Because post-exercise energy expenditure varies between exercise modalities, the magnitude of effect of post-exercise hypoxic exposure may likewise vary, perhaps depending on exercise intensity and the degree of sympathetic stimulation [41]. Additional research investigating sympathetic activity during and after the period of hypoxic exercise recovery is warranted to confirm the mechanistic basis for the observed increase in energy expenditure, and comparisons should be made regarding the magnitude of effect across various exercise modalities.

4.2. Energy Intake

One of the presuppositions behind the 50 kcal mark set by Hill and colleagues was a static energy intake. However, the pioneering work of Jean Mayer in 1956 [4] revealed that, when starting with at least a minimal degree of physical activity, additional caloric expenditure would be accompanied by an increase in energy intake. In light of these findings, the general expectation—one often confirmed in the literature [42]—is that the energy balance equation is dynamic, where altering one variable (e.g., exercise energy expenditure) influences other components of energy balance. Contrary to the increase in energy intake reported by Mayer, we observed a *reduction* in hunger when energy expenditure was increased. Though difficult to isolate, the difference between our findings and those of Mayer may have arisen due to the means of energy expenditure elevation (physical activity vs. environmental stimuli). Regarding the 50 kcal mark, although energy expenditure in hypoxia failed to reach this threshold, it is possible that by reducing hunger, a simulated high altitude recovery does in fact reach the requisite 50 kcal standard invoking meaningful weight management. This conclusion assumes that a reduction in hunger equates to a decrease in energy intake—a connection that was previously reported when *ad libitum* energy intake was recorded at high altitude [43].

One possible explanation for the observed change in appetite is an increased production of the anorexigenic hormone leptin, which is known to be elicited by the high altitude environment [44,45]. While the participants in our study reported a reduction in hunger, we found no difference in leptin concentration between the normoxic and the hypoxic conditions. As such, our findings deviate from those of Tschöp et al. [45] who reported a hypoxia-induced release of leptin. One possible explanation behind the discrepant results may be differences in the duration of hypoxic exposure—where our participants experienced 30 min of hypoxia compared to 22 h of highland exposure in Tschöp et al. [45]. A longer period of hypoxic exposure may, therefore, be necessary to elicit significant changes in leptin. Supporting this idea are data from Kelly et al. [46] who recorded no difference in leptin concentration following 30 min of hypoxia. The time course of leptin release in both normobaric hypoxia and hypobaric hypoxia represents an area of future investigation. In our study, despite no observed changes in plasma leptin concentration after 30 min of simulated high altitude exposure during exercise recovery, participants reported increased satiety and decreased appetite under hypoxic conditions. Consequently, hormones other than leptin likely contributed to the observed changes in appetite following a short stint of simulated highaltitude exposure during exercise recovery.

4.3. Group-Specific Responses to Post-Exercise Hypoxia

Given a similar stimulus, such as relative exercise intensity, the magnitude and effect of sympathoadrenal stimulation can differ between men and women [47,48]. These differences may in part be explained by the presence of estrogen and progesterone, and are known to elicit distinct responses between men and women in physiological processes such as macronutrient metabolism [49]. We investigated the potential relationship between sex differences and the influence of hypoxia on energy balance. Although Camacho-Cardenosa et al. [29] observed a more pronounced ventilatory response in men upon exposure to normobaric hypoxia—suggesting a stronger sympathetic response to hypoxia in men—any difference in sympathetic response that may have occurred between the sexes did not correspond to any significant difference in energy expenditure between men and women in our study. Although acute exercise evokes a similar appetite response in women and men [50], hypoxia is known to affect appetite hormones and may influence hunger and satiety differently in women and men. We recorded no observable differences in hunger and satiety between the two groups, demonstrating a common effect of post-exercise hypoxia on energy balance between the two groups. Additionally, we investigated any potential differences between those who maintained an arterial oxygen saturation $\geq$80% (often used at sea level as the threshold for hypoxia, [51,52]) during altitude exposure compared with those who experienced saturation values <80%. Given the p value of 0.06, a greater

sample size may have revealed that those who better maintained SaO_2 also burned more calories, perhaps through a more robust sympathetic response and accompanying energy expenditure. Similar to the results obtained when stratifying by sex, the hunger response to hypoxia was unaffected by the ability to maintain blood gases above 80% saturation.

4.4. Methodological Considerations

Though our results indicate that simulated high altitude exposure during exercise recovery may serve as a tool to promote energy balance compared to exercise alone, some limitations must be considered. First, we relied on heart rate data to calculate energy expenditure instead of oxygen consumption. The experimental investigation was undertaken as a pilot, proof-of-concept study, and while the heart rate equation we relied upon has been reported to estimate energy expenditure with a great deal of accuracy, utilizing oxygen consumption is more traditionally practiced and commonly recognized for its validity in calculating caloric expenditure. Secondly, because we only tracked participants for 30 min post-exercise, we were unable to determine if food intake was blunted in the face of less subjective hunger elicited by the hypoxic condition. While tracking participants for a longer duration may have revealed that differences in hunger and energy intake were less than reported, a longer tracking of participants could have also revealed a greater magnitude of difference in energy expenditure. At the end of 30 min recovery, heart rate had not yet returned to baseline values in the hypoxic condition. Given a longer period of measurement, the differences in energy expenditure may have exceeded the values we reported. Previous studies found that altitude increases RMR [39] especially through increased sympathetic activity [15], and had we measured RMR the following morning, any observed differences would be of therapeutic relevance [32]. Alongside tracking energy intake, understanding the underlying mechanisms explaining differences in hunger and satiety may be supported by a broader study of appetite hormones. For example, studies measuring CCK and ghrelin have previously established that the production of these appetite hormones may be influenced by high altitude [14]. Evidence also supports a unique macronutrient metabolism in women compared to men, and tracking the flux of circulating macronutrients during hypoxic recovery would offer additional insights into any sex-based responses to simulated high altitude recovery [49]. In line with the previously mentioned limitations, exposing participants to a longer recovery period may further influence appetite hormone production and allow for extended study of their secretion as concentrations change over the course of the recovery period. Finally, by testing women in the follicular phase, we isolated a period when estrogen and progesterone are at their lowest. While the chosen testing window permits confidence that women experienced similar influences of sex hormones, this same testing timeline obscures differences between men and women that might otherwise appear, for example, when estrogen and progesterone levels are elevated [53]. Further studies might investigate the role of menstrual phase and menopause on the observed effects in women, especially considering the role of hormonal changes in menopausal weight gain [54].

4.5. Conclusions

Our results identify hypoxic exposure during exercise recovery as a promising strategy to encourage a healthy body mass regulation. While simulated high altitude exposure alone was previously suggested as a weight maintenance strategy [14], the combination of hypoxia with exercise recovery may produce an amplified effect on energy balance. Given the pilot nature of this study and the reliance on heart rate for indirect calorimetry, future studies should apply this technique to overweight or obese individuals to investigate whether hypoxia bears a universal influence on individuals with various metabolic profiles. Given a deeper understanding for how hypoxic exposure during exercise recovery might encourage healthy body mass regulation, this strategy may serve as a powerful supplement to exercise, and one which would be attainable for the common exerciser with access to a hypobaric or hypoxic chamber—an amenity that is likely to become increasingly pervasive

in exercise facilities throughout the developed world. In conclusion, exposure to a simulated high altitude post-exercise may promote excess energy expenditure compared to recovery at sea level while simultaneously prompting decreases in energy intake, indicating a promising strategy for weight maintenance, especially for those who are unable to maintain a neutral or negative energy balance with exercise alone.

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