# ACUTE AND SHORT-TERM NORMOBARIC HYPOXIC CONDITIONING ON PSYCHO-PHYSIOLOGICAL RESPONSES IN OBESE POPULATIONS

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# Abstract

This thesis investigated the psycho-physiological responses of obese individuals during and following acute and short-term hypoxic conditioning, including both passive and active modalities.

Study one determined psycho-physiological responses to passive hypoxic conditioning ($FiO_2$ = 12.0%) consisting of varying hypoxic and normoxic cycles in obese individuals. It was found that perceptions of breathlessness following short (15 × 2 mins hypoxia/2 mins normoxia) cycles was lowest (-7%) for up to 60 mins post-exposure compared to long cycles (5 × 6 mins hypoxia/6 mins normoxia), whilst the extent of desaturation in arterial oxygen saturation was greater in the latter than the former (-4%). The fndings of this study later informed the interval work/rest duration of exercising in hypoxia for obese individuals.

Study two assessed psycho-physiological responses of trained runners during a perceptually-regulated interval running session (4 × 4 mins at a rating of perceived exertion equal to 16, 3 mins recovery) in hypoxic ($FiO_2$ = 15.0%) and normoxic conditions. The main findings show that a slower treadmill velocity (-6%) was required to maintain a rating of perceived exertion equal to 16 in hypoxia than normoxia. Whilst physiological responses were matched between conditions (i.e., heart rate and muscle oxygenation), exercise-related sensations (i.e., perceived recovery [-21%], motivation [-21%], breathlessness [+22%%], limb discomfort [+11%%] and pleasure [-31%]) were negatively impacted more so during hypoxia compared to normoxia. The findings of this study provided an intial insight regarding the influence of hypoxia on the perceptually-regulated exercise model in trained runners prior to utilisation in an obese population.

Study three assessed psycho-physiological responses of obese individuals during a perceptually-regulated interval walking session (15 × 2 mins walking, 2 mins recovery, based on the findings of study one) in hypoxic ($FiO_2$ = 13.0%) and normoxic conditions. Further,

during an additional third condition, the psycho-physiological responses from hypoxia were isolated with the velocity selected during this trial matched in normoxic conditions. Similar to study three, a slower treadmill velocity (-2%) was required to maintain a rating of perceived exertion equal to 14 in hypoxia than normoxia. Physiological responses were more pronounced during hypoxia compared to normoxia (i.e., higher heart rate [+6%] and lower muscle oxygenation [-6%]), whilst perceptions of limb discomfort were lower (-21%) in the former than the latter. In the absence of hypoxia at the same velocity, perceptions of limb discomfort were matched to perceptually-regulated walking in hypoxia, but the physiological stress was lower (i.e., heart rate [-5%]). The findings of this study provided indication of the acute effects of perceptually-regulated interval walking in hypoxia prior to implementation of this protocol design on a regular, short-term basis.

Study four examined the psycho-physiological responses of obese individuals to a short-term training intervention (utilising the same session protocol of study three, eight sessions in two weeks) in hypoxic ($FiO_2$ = 13.0%) and normoxic conditions. A similar perceptually-regulated velocity, physiological stress (i.e., heart rate) and exercise-related sessions (i.e., perceived recovery, motivation, breathlessness, limb discomfort and pleasure) were recorded during training between conditions. Improvements in perceived mood state (+12%), exercise-self-efficacy (+11%) and energy expenditure (+10%) were reported after training independent of condition, whilst resting blood glucose levels were only enhanced after hypoxic training (-15%).

Collectively, obese individuals may benefit in terms of psycho-physiological responses from exercising at a perceptually-regulated intensity in hypoxia more so than normoxia. These benefits (acute and short-term) could be potentiated largely due to the optimisation of cycle variations of hypoxia/normoxia and exercise/rest durations.

The current work provides several new and novel contributions in relation to this field of research. Firstly, this thesis assesses a combination of psycho-physiological responses regarding hypoxic conditioning, and emphasises their importance for the population studied. Secondly, the optimisation of the cycle length and frequency (i.e., study one) may be a strong predictor for the positive findings following subsequent implementation of this in later studies (i.e., study three and four). Thirdly, lower perceptually-regulated exercise intensities in hypoxia lead to similar or greater acute psycho-physiological responses than normoxia. Finally, psycho-physiological benefits can be achieved from as little as eight interval sessions in two weeks when in hypoxia versus normoxia which may improve adherence.

Practically, short and frequent cycles of hypoxic conditioning are tolerable for obese individuals, and provide larger acute and short-term physiological and metabolic stress. The perceptually-regulated exercise model may be a positive selection of intensity for obese individuals when in hypoxia as this permits the necessary adjustments to external workloads. Positive results from a short-term hypoxic conditioning intervention may aid adherence for further improvements to health in at-risk individuals.

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## List of abbreviations

| | |
|---|---|
| **ANOVA** | Analysis of variance |
| **au** | Arbitrary units |
| **BMI** | Body mass index |
| **bpm** | Beats per minute |
| **cm** | Centimetres |
| **EE** | Energy expenditure |
| **ES** | Effect size |
| **$FeCO_2$** | Fraction of expired carbon dioxide |
| **$FeO_2$** | Fraction of expired oxygen |
| **$F_ICO_2$** | Fraction of inspired carbon dioxide |
| **$FiO_2$** | Fraction of inspired oxygen |
| **h** | Hours |
| **HDL** | High-density lipoprotein |
| **HHb** | Deoxygenated haemoglobin |
| **HIIT** | High-intensity interval training |
| **HR** | Heart rate |
| **$HR_{MAX}$** | Maximum heart rate |
| **HYP** | Hypoxic trial/group |
| **$HYP_{self\text{-}selected}$** | Hypoxic trial at a perceptually-regulated exercise intensity |
| **Hz** | Hertz |
| **IHE** | Intermittent hypoxic exposure |
| **kcal/min** | Kilocalories per minute |
| **kg** | Kilograms |

| | |
|---|---|
| **$kg/m^2$** | Kilograms per metre squared |
| **km/h** | Kilometres per hour |
| **L** | Litres |
| **L/min** | Litres per minute |
| **LDL** | Low-density lipoprotein |
| **LONG** | 5 × 6/6 mins hypoxia/normoxia |
| **LSBU** | London South Bank University |
| **M** | Metres |
| **MEDIUM** | 10 × 3/3 mins hypoxia/normoxia |
| **min(s)** | Minute(s) |
| **min/week** | Minutes per week |
| **mmHg** | Millimetre of mercury |
| **mmol/l** | Millimoles per litre |
| **Ms** | Milliseconds |
| **NHS** | National Health Service |
| **NIRS** | Near-infrared spectroscopy |
| **Nm** | Nanomolar |
| **NOR** | Normoxic trial/group |
| **$NOR_{imposed}$** | Normoxic trial at the velocity selected in hypoxic conditions |
| **$NOR_{self\text{-}selected}$** | Normoxic trial at a perceptually-regulated exercise intensity |
| **$O_2$** | Oxygen |
| **$O_2Hb$** | Oxygenated haemoglobin |
| **RER** | Respiratory exchange ratio |
| **PANAS** | Positive and negative affects schedule |
| **$PO_2$** | Oxygen partial pressure |

| | |
|---|---|
| **Post0** | 0 mins (immediately) after intervention |
| **Post15** | 15 mins after intervention |
| **Post30** | 30 mins after intervention |
| **Post60** | 60 mins after intervention |
| **RPE** | Rating of perceived exertion |
| **S** | Seconds |
| **SD** | Standard deviation |
| **SHORT** | 15 × 2/2 mins hypoxia/normoxia |
| **$SpO_2$** | Arterial oxygen saturation |
| **tHb** | Total haemoglobin |
| **TSI** | Tissue saturation index |
| **$VCO_2$** | Carbon dioxide output |
| **$V_E$** | Volume expired |
| **$V_I$** | Volume inspired |
| **$VO_2$** | Oxygen uptake |
| **$VO_{2MAX}$** | Maximum oxygen uptake |
| **$VO_{2PEAK}$** | Peak oxygen uptake |
| **$vVO_{2MAX}$** | Velocity associated with maximal oxygen uptake |
| **WHO** | World Health Organisation |
| **α** | Alpha |
| **β** | Beta |
| **Δμmol** | Change in micromole |
| **Ml** | Microlitre |
| **°C** | Degrees Celsius |
| **$[La^+]$** | Blood lactate concentration |

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> "*Progress is rarely a straight line. There are always bumps in the road, but you can make the choice to keep looking ahead*."
>
> Kara Groucher

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## Declaration

I declare that the research presented within this thesis is the original work of the author unless stated. This work has been submitted solely for the degree of Doctor of Philosophy to London South Bank University.

Liam Hobbins

24th September 2019

## List of publications

**Hobbins L**, Gaoua N, Hunter S, Girard O. Psycho-physiological responses to perceptually-regulated interval runs in hypoxia and normoxia. *Physiology & Behavior*. 2019b;209:112611.

**Hobbins L**, Girard O, Gaoua N, Hunter S. Acute psychophysiological responses to cyclic variation of intermittent hypoxic exposure in adults with obesity. *High Altitude Medicine & Biology*. 2019a;In print.

**Hobbins L**, Hunter S, Gaoua N, Girard, O. Normobaric hypoxic conditioning to maximize weight loss and ameliorate cardio-metabolic health in obese populations: a systematic review. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*. 2017;313(3):R251-R264.

## Conference proceeding’s

**Hobbins L**, Gaoua N, Girard O, Hunter S. Psycho-physiological responses to perceptually-regulated hypoxic and normoxic interval walking in obese individuals. In. Extreme Environmental Physiology: Life at the Limits, The Physiological Society, Portsmouth, United Kingdom, September 2019.

**Hobbins L**, Hunter S, Gaoua N, Girard O. Psycho-physiological responses to perceptually-regulated interval runs in hypoxia and normoxia. In. European College of Sport Sciences, Prague, Czech Republic, July 2019.

**Hobbins L**, Hunter S, Gaoua N, Girard O. Psycho-physiological responses to perceptually-regulated interval runs in hypoxia and normoxia. In. London South Bank University’s Annual Doctoral Conference, London, United Kingdom, June 2019.

**Hobbins L**, Gaoua N, Girard O, Hunter S. Hypoxic training for health: Here to stay? Practical applications for the ‘real’ world. In. London South Bank University’s Annual Mini Doctoral Conference, London, United Kingdom, April 2019.

**Hobbins L**, Gaoua N, Girard O, Hunter S. Acute psycho-physiological responses to intermittent hypoxic exposure in obese individuals: Effect of cyclical manipulation of varying duration. In. European College of Sport Sciences, Dublin, Republic of Ireland, July 2018.

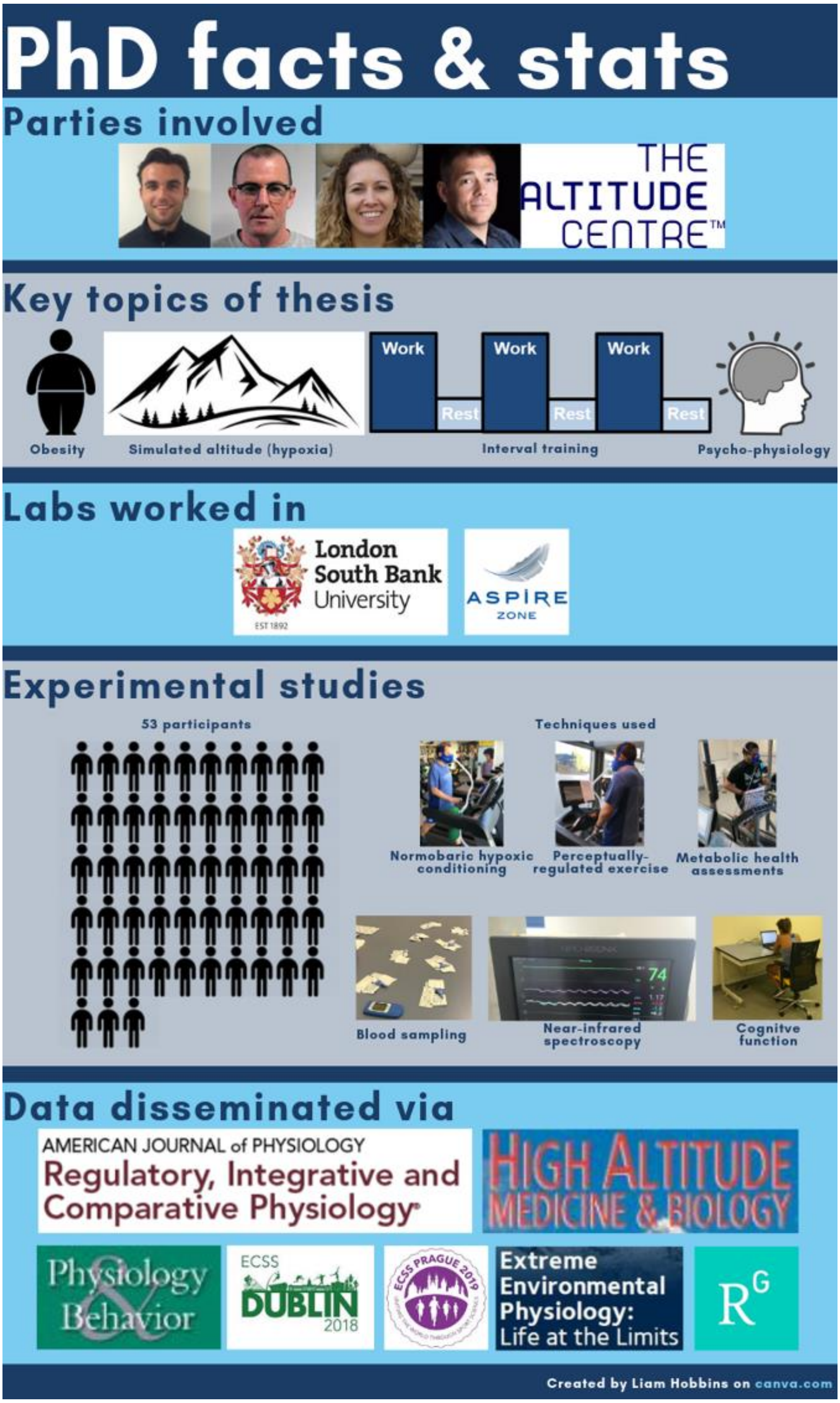
**Hobbins L**, Gaoua N, Girard O, Hunter S. Acute psycho-physiological responses to intermittent hypoxic exposure in obese individuals:

Effect of cyclical manipulation of varying duration. In. London South Bank University's Annual Mini Doctoral Conference, London, United Kingdom, February 2018.

**Hobbins L**, Gaoua N, Girard O, Hunter S. Hypoxic conditioning as a new strategy to treat obese populations. In. London South Bank University's Annual Doctoral Conference, London, United Kingdom, June 2017.

**Hobbins L**. Current research on intermittent hypoxic training and intermittent hypoxic exposure for improving cardio-metabolic markers relating to sports performance. In. The Altitude Centre's Annual Training Masterclass, London, United Kingdom, March 2017.

## Graphical representation of thesis



# PhD facts & stats

## Parties involved

THE ALTITUDE CENTRE™

## Key topics of thesis

Work

Rest

Work

Rest

Work

Rest

Obesity

Simulated altitude (hypoxia)

Interval training

Psycho-physiology

## Labs worked in

London South Bank University

EST 1892

ASPIRE ZONE

## Experimental studies

53 participants

Techniques used

Normobaric hypoxic conditioning

Perceptually-regulated exercise

Metabolic health assessments

Blood sampling

Near-infrared spectroscopy

Cognitve function

## Data disseminated via

AMERICAN JOURNAL of PHYSIOLOGY

Regulatory, Integrative and Comparative Physiology

HIGH ALTITUDE MEDICINE & BIOLOGY

Physiology & Behavior

ECSS DUBLIN 2018

ECSS PRAGUE 2019

Extreme Environmental Physiology: Life at the Limits

RG

Created by Liam Hobbins on canva.com

# 1. General introduction

## 1.1. Obesity

Obesity is labelled as the global epidemic of the 21st century (World Health Organisation, 2003). In the United Kingdom alone, 58% of women and 65% of men are considered to be overweight or obese, i.e., defined as having a body mass index (BMI) of 25–29.9 or ≥30 kg/m$^2$, respectively (National Health Service [NHS], 2016). Compared to the early 1990's, where obesity prevalence was estimated to be ~15%, in today's society there is a 1 in 4 chance (a 10% increase from the 1990's) of an individual becoming obese (NHS, 2016). The economic cost of obesity is profound, with at least £5.1 billion spent on treating this disease (Scarborough et al., 2011). Obesity is a global disease that, as well as economic consequences, has far reaching and damaging impact on the physiological, metabolic and psychological health of individuals (Carroll et al., 2007). Obese individuals carrying out typical daily activities such as stair climbing, prolonged standing and exercise (i.e., walking, running, cycling or resistance training) are more likely to develop negatively impacted movement patterns, subsequently effecting limb-loading and increasing chance of injury compared with healthy weight individuals (BMI = 18.5–24.9 kg/m$^2$) due to excessive weight-carrying (Wearing et al., 2006). This may therefore limit the functional capabilities of those who are obese further reducing activity levels, perpetuating the obesity problem and increasing the risk of related hypokinetic diseases.

## 1.2. Health factors associated with obesity

Obesity is typically caused by a consistently positive energy balance, i.e., greater calories consumed *versus* those expended, which eventually leads to excess fat accumulation (Kayser & Verges, 2013). A consequence of weight gain may also result in elevated blood pressure

(Cooper et al., 2012) and metabolic deficiencies (Kayser & Verges, 2013). Co-morbidities such as cardiovascular disease, hypertension and Type II Diabetes are therefore at greater risk of development in obese populations resulting in the likelihood of higher mortality rates (Guh et al., 2009). Specifically, for every 5-unit increase in BMI >25 kg/m$^2$, overall mortality increases by 29%, vascular mortality by 41% and Diabetes-related mortality by 210% (Apovian, 2016). Given the increased prevalence and the impact of obesity on health, there has been a recognition of the need to reduce obesity prevalence (and its associated health risks) within the scientific, health and medical communities.

### 1.3. Exercise training as a strategy for combating obesity

Aside from bariatric surgery, that is primarily available for the most severe obesity cases (BMI ≥40 kg/m$^2$) (Buchwald et al., 2004), and dietary manipulation/calorie restriction (Gomez-Arbelaez et al., 2017), exercise training is currently proposed as a primary strategy for weight loss. Exercise training may include walking (Fogelholm et al., 2000), running (Marchesi et al., 2015), cycling (Hey-Mogensen et al., 2010), stair climbing (Wong et al., 2008), resistance training (McGuigan et al., 2009) on a regular basis (2–3 times per week, >4 weeks). The NHS (2018) currently recommends >150 mins of moderate aerobic activity (i.e., cycling or brisk walking) per week combined with strength training (targeting all major muscle groups) on two days per week for adults aged 19–64 years to maintain a healthy status. For weight loss to be considered clinically significant, a change of ≥3% in body weight is required (Donnelly et al., 2009). Subsequently, ≤3% change is deemed as weight maintenance over the duration of several months (Stevens et al., 2006). Typically, weight loss is achieved in the first six months of commencing a new exercise programme, but a plateau is then reached and often the weight lost is subsequently regained (Urdampilleta et al., 2012). This also tends to be the case for dietary interventions, whereby, weight regain is highly prevalent (Rolland-Cachera et al., 2004).

Given the inadequacy of current weight management strategies, innovative approaches are warranted to facilitate clinically relevant weight loss and significant improvements in the health and general well-being of overweight and obese populations, beyond that which is being achieved with current interventions.

### 1.4. Normobaric hypoxic conditioning

Hypoxia is defined as a reduced (or insufficient) oxygen ($O_2$) supply to tissues caused by decreases in $O_2$ saturation of arterial blood (Heinonen et al., 2016). Hypoxic conditioning relates to passive (i.e., during rest) or active (i.e., during exercise) exposure to systemic (whole body) and/or local (tissue) hypoxia, resulting in a decrease in arterial oxygen saturation ($SpO_2$) (Lundby et al., 2009). Hypoxic conditioning can be implemented acutely (single exposure) or chronically (multiple exposures over prolonged periods of time).

Normobaric hypoxia (or simulated altitude *via* a reduced inspired $O_2$ fraction [$FiO_2$]), is increasingly popular in no small part due to the increasing number of commercially available devices permitting exposure to hypoxic environments. Primarily, this intervention allows residing at or near sea level and then exposing individuals periodically to hypoxic conditions at rest or during exercising. This is accomplished by breathing through a facemask or spending a period of time in an environmentally controlled chamber/room/tent whereby the $FiO_2$ is typically reduced to 15–12% (equivalent to simulated altitudes of ~2600–4300 m). Due to the systemic nature of normobaric hypoxic exposure and the requirement of oxygen as a means of homeostasis within the human system, responses to this stimulus arise from tissue demand exceeding $O_2$ supply (Lundby et al., 2009). In sedentary overweight males, for instance, passive acute (single 3-hour exposure session) normobaric hypoxic conditioning increased energy expenditure and altered fuel utilisation (decreased glucose and increased lipid oxidation), while further passive hypoxic conditioning (multiple 3-h exposure sessions on seven consecutive days) magnified these metabolic adjustments (Workman & Basset, 2012). For a range of exercise intensities (55–65% of maximal $O_2$ uptake [$VO2_{max}$]/60–70% of maximum heart rate [$HR_{max}$]) performed in hypoxia at similar levels of simulated altitude (~2600 m), it is suggested that active hypoxic conditioning induces specific physiological and metabolic adaptations that do not occur when training in a normoxic environment (Gatterer et al., 2015, Kong et al., 2014, Morishima et al., 2015, Netzer et al., 2008, Wiesner et al., 2009). These positive adaptations are reported to include; increased basal noradrenaline levels (Calbet, 2003), arteriole diameter and peripheral vasodilation (Montero & Lundby, 2016), increased mitochondrial number (Urdampilleta et al., 2012), increased glycolytic enzyme activity (Fenkci et al., 2006), improved insulin sensitivity (Mackenzie et al., 2011), as well as reduced diastolic blood pressure (Shatilo et al., 2008) and leptin levels (Kelly et al., 2010). Such physiological adaptations would in turn improve the metabolic phenotype of obese individuals.

### 1.5. Importance of psycho-physiological measures

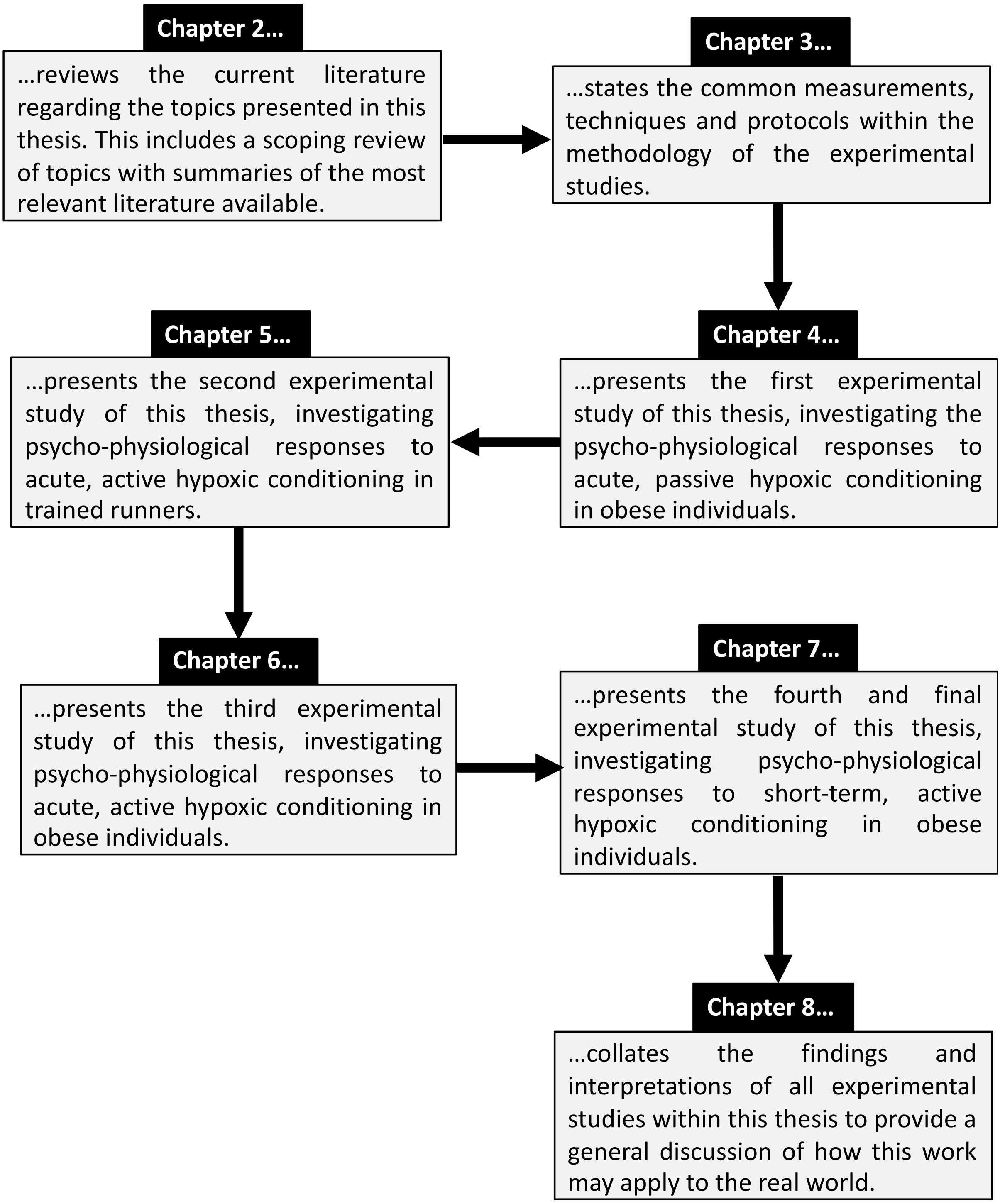
Given the multifaceted negative health effects of obesity, there is a requirement for research to investigate more than only the physiological and metabolic responses to exercise training as a means of combating weight gain and promoting weight loss in obese individuals. Psycho-physiology relates to the perceptions of the outside world from sensations that arise within the body (Miller, 1978). This idea was conceptualised over 100 years ago but is now a growing feature in sports science research. In obese individuals, it is likely that a particular exercise training programme may lead to significant weight loss and improved insulin sensitivity and blood pressure. However, if the exercise training programme is psychologically demanding (i.e., too difficult to complete), it is unlikely that it will promote adherence, regardless of the positive physiological and metabolic outcomes. As such, determining psychological measures in relation to mood and perceptions of exercise are equally important to physiological and metabolic indices when implementing weight loss strategies in obese individuals (Carels et al., 2007). The current absence of psychological factors assessed alongside physiological markers may be one explanation as to why current weight loss strategies (i.e., exercise and/or dietary interventions) are not reducing the global rates of obesity.

### 1.6. Psycho-physiological responses to hypoxic conditioning

To date, investigations of the psycho-physiological responses to hypoxic conditioning in obese individuals are absent. From a physiological and metabolic perspective, passive hypoxic exposure, (3 h continuous exposure, clamped $SpO_2$ = 75%) and active hypoxic conditioning ($FiO_2$ = ~15.0% 60–90 mins running/walking/cycling, three times per week, 4–6 weeks) have shown to increase energy expenditure (Workman & Basset, 2012), decrease blood glucose (Morishima et al., 2014) and insulin levels (Morishima et al., 2015, Wiesner et al., 2009), and promote weight loss (Gatterer et al., 2015, Kong et al., 2013, Netzer et al., 2008) in obese individuals. However, passive hypoxic exposure ($FiO_2$ = 12.5%, 21 day bed rest) has shown to increase depression, tension and confusion in healthy individuals compared to normoxic bed rest (Stavrou et al., 2018). Active hypoxic exposure ($FiO_2$ = 13.0%, 5 mins, self-paced intensity) lead to higher ratings of breathlessness, limb discomfort and overall discomfort (Christian et al., 2014). As highlighted in the previous section, considering psycho-physiological responses in obese individuals is necessary for developing strategies to improve health and promote weight loss. Therefore, it is necessary for further research to investigate the psycho-physiological responses to hypoxic exposure in order to promote adherence and increase the potential therapeutic benefits in obese individuals.

## 1.7. Studies within this thesis

This chapter has outlined the negative impact and co-morbidities of obesity and how exposure to hypoxia may be an alternative means of improving health and promoting weight loss in obese individuals. Although a relatively novel area, findings thus far regarding hypoxic conditioning on cardio-metabolic health responses in an obese population are promising. To build upon the current literature, this thesis is presented in the following format (Figure 1):



**Chapter 2…**

…reviews the current literature regarding the topics presented in this thesis. This includes a scoping review of topics with summaries of the most relevant literature available.

**Chapter 3…**

…states the common measurements, techniques and protocols within the methodology of the experimental studies.

**Chapter 4…**

…presents the first experimental study of this thesis, investigating the psycho-physiological responses to acute, passive hypoxic conditioning in obese individuals.

**Chapter 5…**

…presents the second experimental study of this thesis, investigating psycho-physiological responses to acute, active hypoxic conditioning in trained runners.

**Chapter 6…**

…presents the third experimental study of this thesis, investigating psycho-physiological responses to acute, active hypoxic conditioning in obese individuals.

**Chapter 7…**

…presents the fourth and final experimental study of this thesis, investigating psycho-physiological responses to short-term, active hypoxic conditioning in obese individuals.

**Chapter 8…**

…collates the findings and interpretations of all experimental studies within this thesis to provide a general discussion of how this work may apply to the real world.

**Figure 1.** Overview of chapters presented within the current thesis, including brief aim of the purpose of each chapter.

## 2. Literature review

As eluded to in the previous chapter, utilising hypoxic conditioning in obese populations is a relatively novel area of research. However, the surge in data on this area has led to several reviews of the literature. Recent reviews have investigated the role of hypoxia on energy balance (Kayser & Verges, 2013) and its conditioning effects on several pathologies (Verges et al., 2015), and the impact of variations in $O_2$ availability as a therapeutic intervention for body weight management and cardiometabolic health (Quintero et al., 2010, Ramos-Campo et al., 2019, Urdampilleta et al., 2012, Wee & Climstein, 2015). Overall, these reviews tend to agree that hypoxia (i.e., an environmental condition posing a challenge to homeostasis) may play a significant role in the processes associated with improvements in cardio-metabolic health and the weight loss paradigm. Nevertheless, this was not a general consensus across all literature reviews.

However, the aforementioned reviews are limited in terms of examining the potential impact of passive as well as active hypoxic conditioning on markers of cardio-metabolic health and well-being (Wee & Climstein, 2015). Further, combining the effects of hypoxic conditioning of populations with a multitude of diseases (e.g., cardiovascular and pulmonary) does not provide conclusive evidence in relation to the direct effects of this treatment in obese populations (Verges et al., 2015). Implementation of exercise (in hypoxia and/or normoxia) is an important consideration for improving cardio-metabolic health and promoting weight loss in an obese population (Weston et al., 2014). Due to the mechanical restrictions and weight-loading implications on lower limbs (i.e., on knee and ankle joints), general exercise completion in at-risk populations (i.e., obese, overweight and sedentary) is a larger challenge than for those in a healthy population (Wearing et al., 2006). The exploration of potential benefits of exposure to both passive and active hypoxic conditioning may provide pivotal findings for weight loss and subsequent maintenance strategies. Finally, the manipulation of exercise intensity and assessment of perceptual responses and cognitive function to passive and active hypoxic conditioning have not been reviewed to date, primarily due to a large focus on cardio-metabolic health. These outcomes, in addition to cardio-metabolic health, may have a large impact on the potential acute and short-term positive effects of hypoxic conditioning on the health and well-being of obese individuals. Collective assessment of these outcomes may assist with optimising hypoxic conditioning strategies to treat individuals by covering multiple aspects of health by taking a holistic approach.

Therefore, this chapter aims to narratively review the literature regarding cardio-metabolic health and weight loss responses to passive and active hypoxic conditioning, exercise formats (i.e., intensity and type), perceptual responses and cognitive function in obese populations.

## 2.1. Passive hypoxic conditioning

### *2.1.1. Metabolic responses*

This section relates to metabolic outcomes in response to acute and short-term passive hypoxic conditioning, with an outline of the protocols utilised and results found in Table 2.1. In their study, Workman & Basset (2012) assessed metabolic responses, *via* a 30-min metabolic rate determination test (i.e., assessment of resting energy expenditure [EE]) pre- and post-intervention (acute: single 3 h exposure to hypoxia *via* $SpO_2$ clamp = ~80%, short-term: daily 3 h exposure to hypoxia *via* $SpO_2$ clamp = ~80% for seven consecutive days) in overweight, sedentary males. They found increases in EE following acute (+16%) and short-term (+12%) hypoxic conditioning, as did fat metabolism (+44% and +29%, respectively), whereas glucose metabolism decreased (-31% and -49%, respectively). Collectively, these findings suggest that passive hypoxic conditioning may be an effective modality to induce a shift in fuel utilisation and expend a greater quantity of lipid-based energy stores. To date, such a protocol

**Table 2.1.** Metabolic responses to passive hypoxic conditioning.

| Study | Protocol | Blood glucose | EE | Fat metabolism | Glucose metabolism | Insulin sensitivity | LDL cholesterol | LDL:HDL cholesterol ratio |
|---|---|---|---|---|---|---|---|---|
| Costalat et al. (2017) | *Acute*: 70 mins, $SpO_2$ clamp = 80% | ↓ | | | | | | |
| | *Short-term*: 70 mins, $SpO_2$ clamp = 80% for ten consecutive days. | | | | | | ↓ | ↓ |
| Serebrovska et al. (2019) | *Short-term*: 4x 5 mins hypoxia: $FiO_2$ = 12.0%; 5 mins normoxia, three sessions per week for three weeks. | | | | | ↑ | | |
| Workman & Basset (2012) | *Acute*: single 3 h exposure to hypoxia *via* $SpO_2$ clamp = ~80%. | | ↑ | ↑ | ↓ | | | |
| | *Short-term*: daily 3 h exposure to hypoxia *via* $SpO_2$ clamp = ~80% for seven consecutive days. | | ↑ | ↑ | ↓ | | | |

EE = energy expenditure, HDL = high-density lipoprotein, LDL = low-density lipoprotein, $SpO_2$ = arterial oxygen saturation, ↑ = increased, ↓ = decreased.

has not been employed in an obese population. The potential metabolic stress induced during passive hypoxic conditioning may be advantageous for obese individuals to induce an acute negative energy balance, given the absence of exercise involved. Over a longer duration (>seven days), this may lead to a consistent negative energy balance which may promote measurable weight loss. This is supported by the work of Costalat et al. (2017), whereby, resting glucose concentrations decreased after one passive hypoxic conditioning session (70 mins, $SpO_2$ clamp = 80%). In this study, further positive metabolic health outcomes were achieved (decreased low-density lipoprotein and low-density: high-density lipoprotein [HDL] ratio) after 10 sessions in overweight and obese individuals. However, due to the small experimental group (n = 6) and absence of a control group, the findings of this study should be interpreted with caution. Interestingly, in obese pre-Diabetic (Type II) individuals, insulin sensitivity following an oral glucose load was improved (+40%) following short-term hypoxic conditioning (4 × 5 mins hypoxia: $FiO_2$ = 12.0%/5 mins normoxia, three sessions per week for three weeks) (Serebrovska et al., 2019). The authors concluded from this study that insulin levels of their participants were normalised. Given that the incidence of Type II Diabetes is higher with obesity (Apovian, 2016), this particular finding is highly beneficial for improving metabolic responses to hypoxic conditioning.

### *2.1.2. Cardiovascular responses*

Following on from metabolic responses, this section is comprised of cardiovascular responses to acute and short-term passive hypoxic conditioning, with the protocols and results outlined in Table 2.2. Blood pressure remained unchanged following acute (single 3-h session) and short-term (3-h session per day for 7 days) exposure to a $SpO_2$ of ~80% in sedentary, overweight males (Workman & Basset, 2012). Elsewhere in hypertensive patients, normalisation in blood pressure values were found following short-term passive hypoxic conditioning (3–5 mins hypoxia: $FiO_2$ = 14–10%, interspersed with 3–5 mins normoxia,

**Table 2.2.** Cardiovascular responses to passive hypoxic conditioning.

| Study | Protocol | Mean blood pressure |
|---|---|---|
| Lyamina et al. (2011) | *Short-term*: 3–5 mins hypoxia: $FiO_2$ = 14–10%, interspersed with 3–5 mins normoxia, repeated 4–10 times for upto 20 days. | ↓ |
| Mukharliamov et al. (2006) | *Short-term*: 3–5 mins hypoxia: $FiO_2$ = 14–10%, interspersed with 3–5 mins normoxia, repeated 4–10 times for upto 20 days. | ↓ |
| Workman & Basset (2012) | *Acute*: single 3 h exposure to hypoxia *via* $SpO_2$ clamp = ~80%. | ↔ |
| | *Short-term*: daily 3 h exposure to hypoxia *via* $SpO_2$ clamp = ~80% for seven consecutive days. | ↔ |
| Ziegler et al. (1995) | *Acute*: $FiO_2$ = 15.0%, 60 mins. | ↓ |

$SpO_2$ = arterial oxygen saturation, ↓ = decreased, ↔ = maintained.

repeated 4–10 times for upto 20 days) (Lyamina et al., 2011, Mukharliamov et al., 2006). It could be argued that in sedentary, overweight males with normal blood pressure values, it is unlikely that passive hypoxic conditioning may improve blood pressure compared to hypertensive patients – which may have been the case in the study by Workman & Basset (2012). However, in cases where overweight, hypertensive individuals completed a single session of passive hypoxic conditioning (continuous exposure for 60 mins, $FiO_2$ = 15.0%), blood pressure was significantly decreased after compared to before (Ziegler et al., 1995). Therefore, where necessary, passive hypoxic conditioning may provide a protective effect in individuals who are overweight and hypertensive, but not in overweight, normotensive individuals. Whether this is the case for obese, hyper- and normotensive individuals is unknown, but passive hypoxic conditioning may assist with lowering obesity-associated co-morbidities, such as high blood pressure.

### *2.1.3. Dose*

Quantifying the hypoxic dose during passive conditioning requires evaluating the severity of hypoxia ($FiO_2$), duration and number of cycles, and total exposure time (mins) (Navarrete-

Opazo & Mitchell, 2014). Navarrete-Opazo & Mitchell (2014) reported the following provides potential therapeutic effects: $FiO_2$ = 16.0–9.0%, 1–10 mins cycles repeated 12–15 times per day, and upto 12 h entire duration of the protocol (Figure 2.1.A). Contrastingly, passive hypoxic conditioning protocols that elicit potential deleterious effects (i.e., obstructive sleep apnoea) have the following characteristics: $FiO_2$ = 13.0–2.0%, 6 s–4 h cycles repeated 48–2400 times per day, and up to 24 h in total (Figure 2.1.B). The hypoxic severity (i.e., $FiO_2$) and cycles per day appear to be the most significant factors for potential therapeutic effects, with moderate hypoxia and low cycle numbers offering the most positive outcomes (Navarrete-Opazo & Mitchell, 2014). This claim is based upon results from double-blind, clinic-based trials including patients with chronic obstructive pulmonary disease, showing that improvements in cardio-metabolic health occurred following short-term hypoxic conditioning including short, frequent cycles (3–5 mins hypoxia: $FiO_2$ = 15.0–12.0%, interspersed with 3–5 mins normoxia, repeated 5–9 times for 15 days) compared to baseline (Burtscher et al., 2009, Haider et al., 2009). There is a lack of data investigating further potential therapeutic responses to passive hypoxic conditioning in obese individuals, given the already established advantages of this strategy, particularly on metabolic responses thus far reported in the literature.

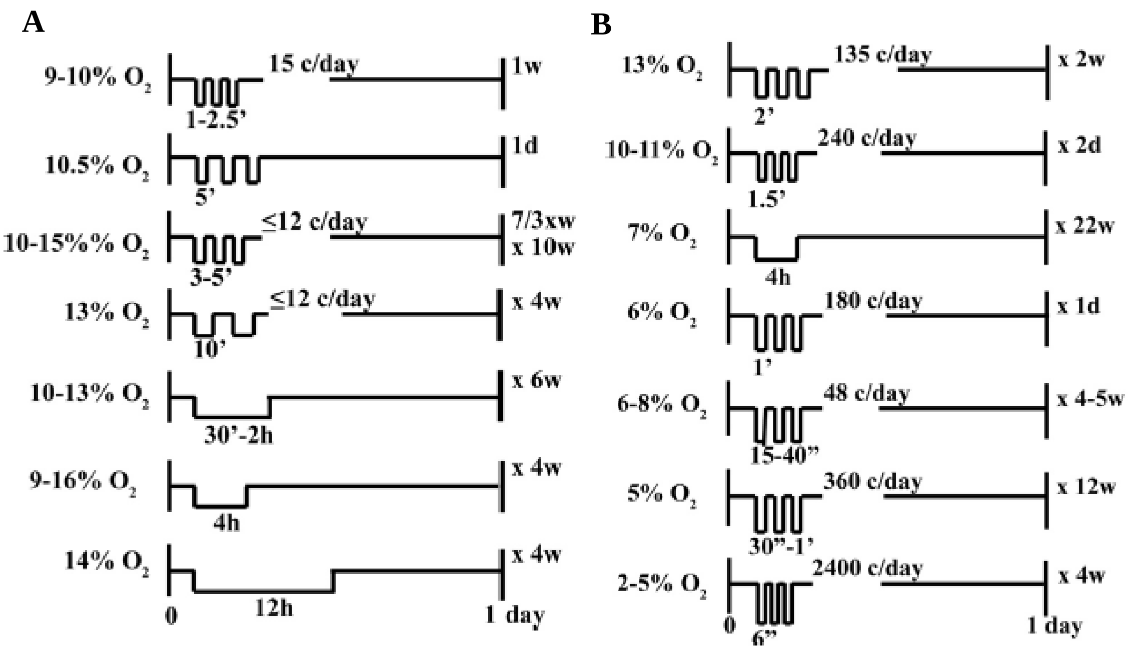


**Figure 2.1.** Therapeutic (A) and deleterious (B) effects realised from varying factors, such as the severity of hypoxia, duration and number of cycles, and total exposure time within passive hypoxic conditioning protocols (Navarrete-Opazo & Mitchell, 2014).

## 2.2. Active hypoxic conditioning

### *2.2.1. Metabolic responses*

The present section reviews the literature on chronic metabolic responses to exercise (typically endurance-based) combined with hypoxic exposure, carried out over a long-term period (≥four weeks). Intervention details and main findings can be found in Table 2.3. Netzer et al. (2008) reported greater enhancements in triglycerides, total and HDL cholesterol in those whom completed 8 weeks training for 90-min at 60% of $HR_{MAX}$ in hypoxic *versus* normoxic conditions three times per week. In other studies, no change has been found in both the hypoxic and normoxic groups for triglycerides, total cholesterol and HDL whilst carrying out a similar exercise intensity range and duration over 4–6 weeks (Morishima et al., 2015, Wiesner et al., 2009, Klug et al., 2018). Morishima et al. (2015) also reported that glucose concentrations decreased in both the hypoxic (-8%, $FiO_2$ = 15.0%) and normoxic (-7%) group following

**Table 2.3.** Metabolic responses to active hypoxic conditioning.

| Study | Protocol | Blood glucose | Fasting insulin levels | Fat metabolism | HDL cholesterol | Postprandial energy expenditure | Total cholesterol | Triglycerides |
|---|---|---|---|---|---|---|---|---|
| Klug et al. (2018) | *Chronic*: 60 mins treadmill exercise at 60% $VO_{2MAX}$, three times per week for six weeks, $FiO_2$ = 15.0%. |  |  | ↑ | ↔ | ↑ | ↔ | ↔ |
| Morishima et al. (2015) | *Chronic*: 60 mins cycling at 65% $VO_{2MAX}$, three times per week for four weeks, $FiO_2$ = 15.0%. | ↓ | ↓ |  | ↔ |  | ↔ | ↔ |
| Netzer et al. (2008) | *Chronic*: 90-min at 60% of $HR_{MAX}$ three times per week for eight weeks, $FiO_2$ = 15.0%. |  |  |  | ↑ |  | ↑ | ↑ |
| Wiesner et al. (2009) | *Chronic*: 60 mins cycling at 60% $VO_{2MAX}$, three times per week for four weeks, $FiO_2$ = 15.0%. | ↓ | ↓ |  | ↔ |  | ↔ | ↔ |

HDL = high-density lipoprotein, $HR_{MAX}$ = maximal heart rate, $VO_{2MAX}$ = maximal oxygen uptake, ↑ = increased, ↓ = decreased, ↔ = maintained.

the intervention (60 mins cycling at 65% $VO_{2MAX}$, three times per week for four weeks). These findings are interesting as all intervention groups (i.e., participants allocated to hypoxic conditioning) exercised under the same hypoxic level ($FiO_2$ = 15.0%) and completed the same type of exercise at an 'absolute' intensity (i.e., based on a percentage of $HR_{MAX}$ or $VO_{2MAX}$) determined in the respective environmental condition. Based on this data, it appears that further improvements in metabolic markers such as triglycerides, total cholesterol and HDL with hypoxic conditioning would require an intervention of more than 4 weeks in duration for positive effects to occur.

In two studies, reduced fasting insulin concentration have been found in both hypoxic ($FiO_2$ = 15.0%) and normoxic training (60 mins, moderate intensity, 3 times per week, for 4 weeks) groups after the intervention (hypoxia: -37%, normoxia: -33% [Wiesner et al., 2009]; hypoxia: -22%, normoxia: -36% [Morishima et al., 2015]). Although non-significant, baseline assessment in both studies of insulin concentrations were ~2 au larger in the hypoxic compared to normoxic group. Therefore, this may explain the insignificant effect of the hypoxic stimulus as those in the normoxic group started the intervention at a lower insulin concentration.

Finally, postprandial EE and fat metabolism was greater following active hypoxic conditioning (60 mins treadmill exercise at 60% $VO_{2MAX}$, three times per week for six weeks) compared to normoxia in males with metabolic syndrome (Klug et al., 2018). An increased postprandial EE following active hypoxic conditioning could be considered particularly beneficial given that obese individuals typically have a lower postprandial EE than healthy individuals (Bessard et al., 1983). The increase in this specific metabolic response to active hypoxic conditioning may result in a greater tendency for a negative energy balance, and it is speculated this this response arises due to the positive actions exercising in hypoxia has on fat metabolism (Kelly & Basset, 2017). However, even though the participants with metabolic syndrome in the study by Klug et al. (2018) were obese, it is unknown whether similar increases in postprandial energy expenditure and fat metabolism occur in obese individuals without metabolic syndrome. It could be argued that the improvements stated here would be greater in obese individuals with less metabolic complications, due to a better functioning metabolic system, but this cannot be concluded based on the present data.

### *2.2.2. Cardiovascular responses*

Following on from metabolic responses, this section reviews cardiovascular responses to chronic active hypoxic conditioning interventions. Protocols and results can be found in Table 2.4. Hypertension is extremely prevalent in obese populations, causing an increased strain on an already laboured cardiovascular system (Kotchen, 2010). Kong et al. (2013) found improvements in systolic (-8%) and diastolic (-7%) blood pressure after active hypoxic conditioning (cardiovascular- [60–70% $HR_{MAX}$] and strength- [40–50% one repetition maximum] based exercise, 22 h over four weeks) compared to normoxia. Notably, the participants in the hypoxic group completed 6 h of the weekly training schedule in a hypoxic environment (type of exercise session carried out in hypoxia unknown), with the remainder carried out in normoxic conditions. Whereas, those who carried out all of the 22 h training load in normoxic conditions had less improvement in systolic (-3%) and diastolic (-1%) blood pressures. Compared to the normoxic group, Wiesner et al. (2009) reported a similar reduction in systolic (-2% *versus* -2%) but greater reduction in diastolic (-4% *versus* -1%) blood pressures in the hypoxic group over a similar duration of 4 weeks, yet with a reduced volume of exercise (180 mins per week). Morishima et al. (2015) compared a four week hypoxic conditioning intervention (60 mins cycling at 65% $VO_{2MAX}$, three times per week) to a two week duration (same exercise duration and intensity, six sessions per week) and found that the improvements in functional fitness (i.e., $VO_{2MAX}$) and mean blood pressure after both training programmes were similar. All in all, active hypoxic conditioning demonstrates more supportive evidence for improved blood pressure responses compared to active normoxic periods. The mechanism behind this improvement is said to involve enhanced vascular endothelial growth factor transcription leading to improved human vasculature control and capillary action (Yang et al., 2015). Importantly, it could be argued that the positive cardiovascular effects realised after a short-term hypoxic conditioning intervention occur to a similar or greater extent as longer-term active hypoxic conditioning and when in normoxic conditions. This is supported by findings showing a lack of further improvement in systolic and diastolic blood pressure assessed after five weeks compared to eight months of combined passive and active hypoxic conditioning (90-min cardiovascular-based exercise at 65–70% $HR_{MAX}$, $FiO_2$ = 14.0%, followed by 90-min passive hypoxic conditioning, $FiO_2$ = 12.0%, twice per week) and normoxia in obese individuals (Gatterer et al., 2015). Therefore, more time-efficient active hypoxic conditioning strategies (i.e., lower total duration, more sessions per week) could outweigh the positive effects reported following chronic active hypoxic conditioning (≥four weeks) on cardiovascular responses of obese individuals.

Reductions in HR, for a given submaximal exercise workload, have been observed for both hypoxic (-18%, 6 h $FiO_2$ = 15.0%) and normoxic (-20%) groups post-intervention (cardiovascular- [60–70% $HR_{MAX}$] and strength- [40–50% one repetition maximum] based exercise, 22 h over four weeks) (Kong et al., 2013). In other studies, no change in HR during an exercise test before and after the intervention period was found in the hypoxic ($FiO_2$ = 15.0%) or normoxic group (60 mins treadmill exercise or cycling at 60–65% $VO_{2MAX}$, three times per week for 4–6 weeks) (Morishima et al., 2015, Wiesner et al., 2009). It could be suggested that due to obese humans having a lower baseline fitness level compared to athletic and healthy populations, it is likely that most forms of regular exercise training will lead to an improved cardiovascular response during exercise, *via* assessment of HR. Arguably, adding in an additional stimulus such as hypoxia likely reduces the potential of an increased cardiovascular response, and therefore, be less beneficial than the same workload in normoxic conditions.

**Table 2.4.** Cardiovascular responses to active hypoxic conditioning.

| **Study** | **Protocol** | **Heart rate** | **Mean blood pressure** | **$VO_{2MAX}$** |
|---|---|---|---|---|
| Kong et al. (2013) | *Chronic*: cardiovascular- [60–70% $HR_{MAX}$] and strength- [40–50% one repetition maximum] based exercise, 22 h (6 h in hypoxia, $FiO_2$ = 15.0%) over four weeks | ↓ | ↓ |  |
| Gatterer et al. (2015) | *Chronic*: 90-min cardiovascular-based exercise at 65–70% $HR_{MAX}$, $FiO_2$ = 14.0%, followed by 90-min passive hypoxic conditioning, $FiO_2$ = 12.0%, twice per week |  | ↓ |  |
| Morishima et al. (2015) | *Short-term*: 60 mins cycling at 65% $VO_{2MAX}$, six times per week for two weeks. $FiO_2$ = 15.0%. |  | ↓ | ↓ |
|  | *Chronic*: 60 mins cycling at 65% $VO_{2MAX}$, three times per week for four weeks, $FiO_2$ = 15.0%. | ↔ | ↓ | ↓ |
| Wiesner et al. (2009) | *Chronic*: 60 mins cycling at 60% $VO_{2MAX}$, three times per week for four weeks, $FiO_2$ = 15.0%. | ↔ | ↓ |  |

$HR_{MAX}$ = maximal heart rate, $VO_{2MAX}$ = maximal oxygen uptake, ↓ = decreased, ↔ = maintained.

### *2.2.3. Weight loss*

Weight loss, as defined by a decrease of ≥3% in total body weight (Donnelly et al., 2009), is the focus of the final active hypoxic conditioning section. Training intervention details and primary outcomes of studies included within this section can be found in Table 2.5. Kong et al. (2013) reported significantly greater reductions in total body weight (-7%) in those who completed 6 h of hypoxic conditioning (consisting of cardiovascular- [60–70% $HR_{MAX}$] and strength- [40–50% one repetition maximum] based exercise, 22 h over four weeks) compared to those in the normoxic group (-4%). Netzer et al. (2008) reported significant reductions in total body weight and a tendency of a lower BMI in those who completed active hypoxic conditioning (90-min at 60% of $HR_{MAX}$, three times per week for eight weeks), which did not occur in the normoxic group (i.e., no change). In another study, no change was found in BMI and fat mass following both the hypoxic ($FiO_2$ = 15.0%) and normoxic intervention (moderate-intensity cycling, 3 times per week, 4 weeks), but the normoxic group did lose slightly more weight after the intervention compared to those in the hypoxic group (-1% *versus* -0.5%, respectively) (Morishima et al., 2015). Camacho-Cardenosa et al. (2018) reported larger improvements in body fat content and muscle mass following 12 weeks of high-intensity interval training (aerobic intervals: 3 mins at 90% maximal power output/3 mins at 55–65% maximal power output, sprint intervals: 30 s all out/3 mins at 55–65% maximal power output, 3 sessions per week for 12 weeks) in hypoxia ($FiO_2$ = 17.2%) in reference to normoxia. Overall, improvements in weight, BMI and individual tissue mass have been found following active hypoxic conditioning (moderate-intensity cardio-based exercise, 3 sessions per week, 4–12 week duration) but to a lesser extent in normoxia. The exact mechanism behind greater improvements in body composition following active hypoxic conditioning in obese individuals has not been established to date, but it has been suggested that this may potentially occur to a lower energy intake as reported during altitude sojourns (Westerterp-Plantenga et al., 1999), and linked to greater appetite regulation *via* acylated ghrelin (Matu et al., 2017).

**Table 2.5.** Weight loss responses to active hypoxic conditioning.

| Study | Protocol | BMI | Fat mass | Muscle mass | Total body weight |
|---|---|---|---|---|---|
| Camacho-Cardenosa et al. (2018) | *Chronic*: aerobic intervals: 3 mins at 90% maximal power output/3 mins at 55–65% maximal power output, sprint intervals: 30 s all out/3 mins at 55–65% maximal power output, 3 sessions per week for 12 weeks, $FiO_2$ = 17.2%. |  | ↓ | ↑ |  |
| Kong et al. (2013) | *Chronic*: cardiovascular- [60–70% $HR_{MAX}$] and strength- [40–50% one repetition maximum] based exercise, 22 h (6 h in hypoxia, $FiO_2$ = 15.0%) over four weeks |  |  |  | ↓ |
| Netzer et al. (2008) | *Chronic*: 90-min at 60% of $HR_{MAX}$ three times per week for eight weeks, $FiO_2$ = 15.0%. | ↓ |  |  | ↓ |
| Morishima et al. (2015) | *Chronic*: 60 mins cycling at 65% $VO_{2MAX}$, three times per week for four weeks, $FiO_2$ = 15.0%. | ↔ | ↔ |  |  |

BMI = body mass index, $HR_{MAX}$ = maximal heart rate, $VO_{2MAX}$ = maximal oxygen uptake, ↓ = decreased, ↔ = maintained.

## 2.3. Exercise format

### *2.3.1. Fixed-intensity*

A number of studies in this review mention a reduced workload of participants carrying out moderate-intensity, continuous exercise in hypoxia compared to those in normoxia (Morishima et al., 2015, Wiesner et al., 2009), which has also been proposed elsewhere when clamping the metabolic demand (Girard et al., 2016). Implementing an intensity clamp (i.e., HR, rating of perceived exertion [RPE], metabolic equivalents etc.) may be more appropriate for overweight and obese individuals since the main outcome for carrying out exercise is health-, not performance-related. Therefore, identifying a metabolic equivalent target, for example, could be better tailored to the goal of an obese individual exercising compared to a percentage of $VO2_{MAX}$ or $HR_{MAX}$. Further achieving the '*target clamp*' will require a lower absolute exercise intensity in hypoxia compared to normoxia, as demonstrated by Wiesner et al. (2009). For example, cycling at 100 Watts in hypoxic conditions will create a matched or greater physiological stress (i.e., increased HR, cardiac output) on the human body compared to the same absolute intensity in normoxic conditions; thus inducing a higher internal (physiological) load for a lower external (power output) load (Figure 2.2.). Further research of this area is required to validate this claim and differentiate the effect of adding hypoxia in comparison to the effect of exercising at different intensities. It could be that, clamping the metabolic demand (i.e., working at a given relative exercise intensity in hypoxia *versus* normoxia) may be beneficial for obese populations. Arguably, the musculo-skeletal system load is likely reduced in $O_2$-deprived environments and thereby could prevent further damage to joints, tendons and ligaments during locomotor activities (e.g., outdoor or treadmill walking) (Girard et al., 2016).

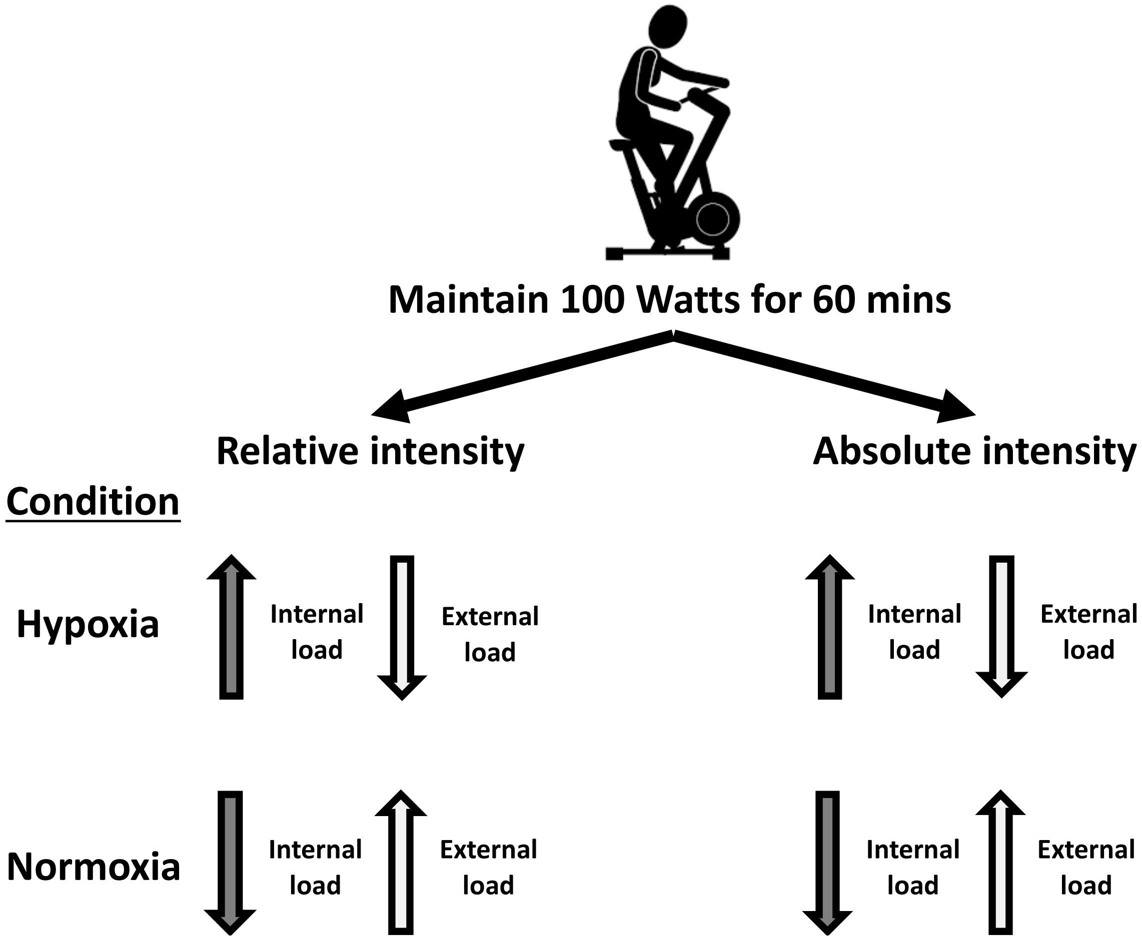


**Figure 2.2.** Visual representation regarding the proposed effects on external and internal loads during exercise (e.g. cycling at 100 Watts) in hypoxia and normoxia based on the work by Wiesner et al. (2009) and Girard et al. (2016).

### *2.3.2. Perceptually-regulated intensity*

To potentially improve the implementation of exercise training in obese individuals, a perceptually-regulated exercise intensity may be more advantageous compared to a fixed-intensity. Perceptually-regulated exercise, also known as clamped-/fixed- RPE, is a model popularised by Tucker (2009). Essentially, the individual carrying out the exercise is constantly receiving internal feedback (i.e., perceptions) regarding the current intensity, and then making immediate adjustments to the intensity where necessary (i.e., increasing, maintaining or decreasing). The expected exercise duration, physiological status and previous competitive experiences of the individual provide the necessary information for the perceptually-regulated intensity to be selected (Figure 2.3.). During short-term active hypoxic conditioning (60-min walking at a preferred velocity, three sessions per week for three weeks), obese individuals selected a lower walking velocity than normoxia (-7%) but both conditions were perceived as a similar intensity (RPE = 10) (Fernandez-Menendez et al., 2018). Further, the increases in the velocity that was preferred by obese individuals increased across the three weeks in both conditions (+8%). Interestingly, it has been shown that when an exercise intensity is increased by 10% above the preferred level in normoxia, perceived pleasure of overweight women is significantly lower (Ekkekakis & Linds, 2006). Given the well-established added physiological stress of exercising at a fixed-intensity in hypoxic compared to conditions (Heinonen et al., 2016), it is tenable that a perceptually-regulated exercise intensity may permit the required adjustments (i.e., decreases in velocity) where necessary (i.e., when the intensity rises above the perceptually-regulated target). It should be of interest for future studies to investigate the manipulation of the external workload which may provide a similar internal workload that could make exercise more enjoyable and increase adherence in obese populations.

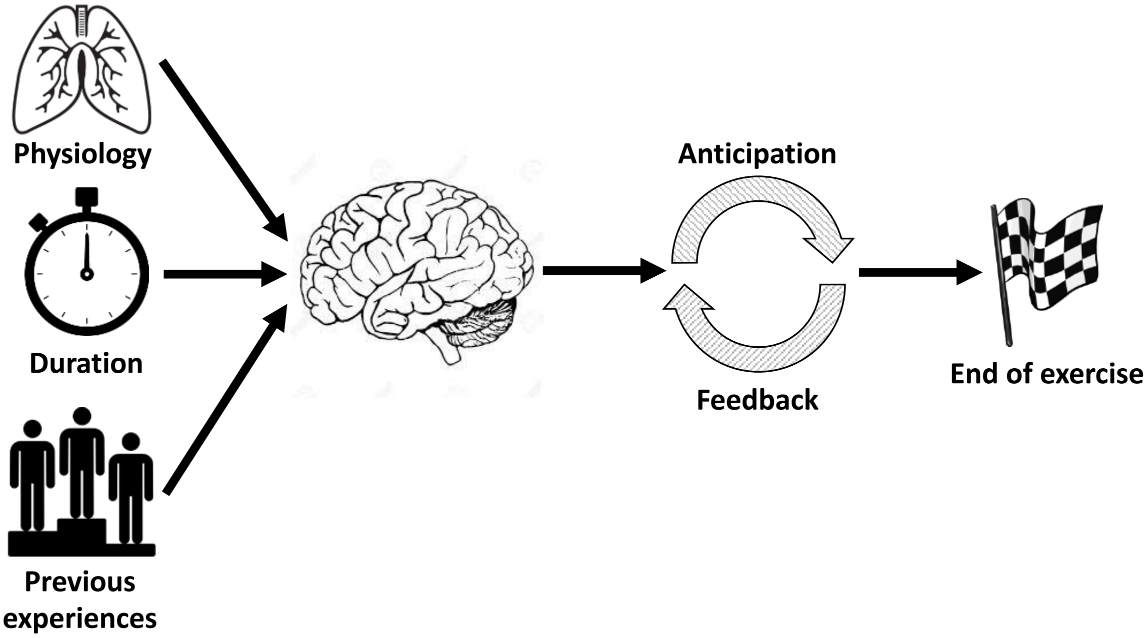


**Figure 2.3.** Visual representation the perceptually-regulated exercise model adapted from Tucker et al. (2009).

### *2.3.3. Type*

In line with current American College of Sports Medicine (Donnelly et al., 2009) and UK NHS recommendations (NHS, 2016), the reviewed literature here suggests that a moderate-intensity, continuous exercise training programme (60–75% $HR_{MAX}$ for 60–90 mins, 3 times per week for 4–6 weeks) is the recommended method to achieve weight loss. However, even though this is not recommended by health-governing bodies, a growing body of literature is indicating that implementation of high-intensity interval training (HIIT) (3–5 sets of high-intensity exercise periods at 75–95% $HR_{MAX}$ for 2–5 mins interspersed with shorter recovery periods of 2–3 mins) in obese populations is beneficial (Gibala et al., 2012, Jelleyman et al., 2015, Ramos et al., 2015, Ramos et al., 2016, Weston et al., 2014, Wewege et al., 2018). Not only is this form of exercise more time- and metabolically-efficient (Little et al., 2014), but would also be more beneficial for weight loss compared to moderate-intensity in normoxia. This is due to potentially similar, if not greater, clinical benefits to health, including improvements in body composition, physical activity, fasting blood glucose and insulin sensitivity (Dalzill et al., 2014), with body composition improvements relating directly to decreases in abdominal and visceral fat tissues (Maillard et al., 2018).

In prescribing HIIT, a careful manipulation of work/rest ratios depending on the aim of the session (aerobically *versus* anaerobically-based responses) is needed. However, there currently is no general consensus regarding the most appropriate interval work/rest duration for obese populations carrying out HIIT. Camacho-Cardenosa et al. (2018a & b) employed 12 weeks of high-intensity interval training (3 sessions per week), consisting of aerobic (3 mins at 90% $Watt_{MAX}$/3 mins at 55–65% $Watt_{MAX}$) and anaerobic (30 s all out/3 mins at 55–65% $Watt_{MAX}$) intervals in hypoxic ($FiO_2$ = 17.2%) and normoxic conditions. Both of these studies revealed that there were no differences in metabolic health markers between the aerobic and anaerobic intervals when carried out in hypoxia, but completing the intervals in hypoxia lead to reduced body fat and increased muscle mass over normoxia (Camacho-Cardenosa et al., 2018a & b). Elsewhere, an anaerobic-focused HIIT program (60 × 8 s maximal sprint, 12 s recovery, four sessions per week for five weeks) led to improved cardiorespiratory fitness of young, overweight females more so when carried out in hypoxia ($FiO_2$ = 15.0%) compared to normoxia (Kong et al., 2017). Although it seems that HIIT in hypoxia leads to more substantial improvements in metabolic and cardiovascular responses relative to normoxia, there is a clear lack of assessment of perceptual responses, or exercise-related sensations, to this type of training in obese populations.

### 2.4. Perceptual responses

A large, and often underestimated, factor in achieving weight loss is related to psychological behaviours. Exercising regularly requires motivation and enjoyment to maintain adherence (Kong et al., 2016a). At present, pleasure-displeasure responses of exercising at a high-intensity in normoxic conditions are varied with both positive affects (Martinez et al., 2015) and negative moods (Muller et al., 2011) reported in comparison to moderate-intensity continuous exercise. It has been shown that even when RPE is elevated, acute HIIT (8 × 1-min at 90% maximal aerobic speed/75 s recovery) does not elicit unpleasant sensations compared to moderate-intensity interval training (9–12 × 1-min at 90% ventilatory threshold distance matched to HIIT/75 s recovery), whilst greater post-exercise enjoyment is present in HIIT (Malik et al., 2017). Implementing such affect-perceptual measurements would significantly aid levels of adherence to achieve weight loss through long-term interventions. Interestingly, Ekkekakis & Linds (2006) concluded that enjoyment was reduced when obese populations walked at an imposed exercise intensity 10% greater than a self-selected speed. It remains to be verified whether implementation of self-selected speeds during shorter work periods in hypoxia would be more applicable in an obese population, as previously reported (Ekkekakis

& Linds, 2006, Hills et al., 2006). This type of investigation does not exist during and following hypoxic conditioning of obese humans. Therefore, the remainder of the current section of the literature review will define specific perceptual responses and their postulated mechanisms, as well as perceptual responses to passive and active hypoxic conditioning in healthy and athletic populations.

### *2.4.1 Definitions and mechanisms of perceptual responses*

RPE, a popular and well-used assessment in sports science, is utilised to determine subjective ratings of whole-body perceived exertion during exercise (Borg et al., 1987). Importantly, there are several localised contributors to this rating, such as perceived breathlessness and limb discomfort. Perceived breathlessness is said to be regulated by the force applied to one's chest *via* respiration, and subsequent visual movement of the chest area (Campbell & Howell, 1963). Perceived limb discomfort results from increased sympathetic vasoconstrictor outflow, causing reduced blood flow to locomotor muscles and locomotor muscle fatigue (Dempsey et al., 2006). In addition to the major contributors to overall RPE, there are several other measures such as perceived recovery, motivation, pleasure, mood state, affects and exercise self-efficacy that could be argued as equally important for determining perceptual responses to exercise. For example, perceived recovery and mood state involve an integration of physiological, psychological and emotional responses (Hardy & Rejeski, 1989, Laurent et al., 2011). Generally, these perceptual responses are modulated *via* receipt of afferent signals to the brain, whilst certain measures of perception may outweigh others dependent on the task (i.e., exercise) being carried out (Hampson et al., 2001).

At the central level, cerebral oxygenation is hampered during high-intensity exercise in normoxia and may explain perceptions of increased fatigue and decreased recovery (Monroe et al., 2016). It has been shown that both passive (Chacaroun et al., 2017) and active (Chacaroun et al., 2018) hypoxic conditioning decreases cerebral oxygenation of the prefrontal cortex in reference to normoxia of healthy individuals. Therefore, it could be suggested that perceptual responses may be hindered during hypoxic conditioning of obese individuals as reflected in decreased cerebral oxygenation, which may perpetuate early onset fatigue and worsened sensations of breathlessness and limb discomfort in particular compared to normoxia. However, this type of investigation has not been carried out thus far, but the potential findings would assist in understanding psycho-physiological responses to hypoxic conditioning in obese individuals and may permit optimisation of hypoxic conditioning strategies.

### *2.4.2. Perceptual responses in general to hypoxic conditions*

During chronic passive hypoxic conditioning (21 days bed rest, $FiO_2$ = 12.5%), healthy males felt more depressed, confused and tense after 14 and 21 days compared to baseline (Stavrou et al., 2018). Interestingly, findings from the same group showed that a shorter passive hypoxic conditioning protocol (10 days confinement, $FiO_2$ = 12.5%) had no impact on perceptual measurements (Stavrou et al., 2015). Overall, it is likely that chronic passive hypoxic conditioning (i.e., continuous exposure) will not positively increase perceptual responses in comparison to normoxia given the well-established negative implications this has on the human system (Navarette-Opazo & Mitchell, 2014). Alternatively, a cyclical modality of passive hypoxic conditioning may induce positive perceptual responses, perhaps *via* re-oxygenation phases to increase cerebral oxygenation as discussed in the previous section (Urdampilleta et al., 2012).

During active hypoxic conditioning, maximal (Brocherie et al., 2017, Christian et al., 2014) and sub-maximal (Christian et al., 2014) cycling lead to worsened perceptions of overall discomfort, breathlessness and limb discomfort in elite and non-elite athletes compared to normoxia. The differences in protocols (maximal cycling: 4 × 5 × 5 s maximal sprints/25 s passive recovery, 5 min rest, first of six sessions, sub-maximal cycling: 5 mins of continuous cycling at an RPE of 3 out of 10) and similarity in perceptual responses suggest that these findings are not task-dependent (i.e., duration of exercise), rather dependent on the hypoxic stimulus. Interestingly, the exercise intensity prescribed during these sessions was not fixed, but rather perceptually-regulated to reach a maximal (Brocherie et al., 2017) or relative effort of RPE (Christian et al., 2014). Jeffries et al. (2019) recently reported that decreases in $SpO_2$ was one of the reasons why healthy males were unable to maintain a continuous cycling bout at an RPE of 16 out of 20 when in moderate ($FiO_2$ = 15.2%) and severe ($FiO_2$ = 11.4%) hypoxia compared to normoxia. Overall, it appears that perceptual responses to current passive and active hypoxic conditioning strategies in healthy and athletic individuals is generally perceived as more demanding compared to normoxia. Whether this is the case for obese individuals is not quite understood but an important consideration for the therapeutic usefulness of hypoxia to target psycho-physiological responses and weight loss.

### 2.5. Cognitive function

Cognitive function refers to the processing, integration, storage and retrieval of information, including perception, attention, memory and executive function (Smith et al., 2011). Although the exact mechanisms are not understood at present, there is a strong positive relationship with increasing body weight and impaired cognitive function (Smith et al., 2011). For example, Walther et al. (2010) showed that obese women had significantly lower scores in tests of executive function compared with healthy women in normoxia at rest. This may have negative consequences on everyday life, such as judgements, decisions and perceptions, leading to greater risky behaviours in at-risk individuals (Sternberg et al., 2013).

The effects of hypoxic conditioning on cognitive function is a relatively new area with unequivocal findings. It has been reported that executive function is negatively affected following passive (10 mins) and active (10 mins continuous moderate-intensity recumbent cycling) hypoxic ($FiO_2$ = 13.5%) conditioning compared to normoxia in healthy individuals

(Ochi et al., 2018). In contrast, cognitive function was better (i.e., faster reaction time) after active hypoxic conditioning ($FiO_2$ = 13.5%, 60 mins continuous moderate-intensity running) compared to normoxia in healthy males (de Aquino-Lemos et al., 2016). There has been no study that has investigated the potential influence of hypoxic conditioning in obese individuals on cognitive function. It is unlikely that acute or short-term passive and active hypoxic conditioning could directly improve cognitive function in obese individuals due to the demanding environmental stimulus limiting function of an already diminished system (Heinonen et a., 2016, Walther et al., 2010). However, given the aforementioned reports of greater weight loss found after chronic active hypoxic conditioning compared to normoxia (Kong et al., 2013, Netzer et al., 2008), this could in turn result in improvements in cognitive function of obese individuals. To date, this has not been investigated, but the potential findings could assist with the decision making and lifestyle choices of obese individuals if cognitive function were to be improved following hypoxic conditioning. Through dietary control (i.e., calorie restriction) and increased physical activity, it has been shown that obese and overweight adults achieved significant weight loss and improvements in attention and memory compared to baseline (Veronese et al., 2017). Hypothetically, the improvements in cognitive function could be greater following hypoxic conditioning compared to normoxia in the presence of weight loss due to the potential to exercise at a lower workload in hypoxia for obese individuals to achieve weight loss (Girard et al., 2016, Wiesner et al., 2009). Investigations surrounding this claim could lead to improvements in psycho-physiological responses to hypoxic conditioning and subsequent adherence to a short-term intervention.

## 2.6. Conclusions

The findings of this review in obese populations suggest that a) passive hypoxic conditioning could lead to increased EE (+12–16%), while active hypoxic conditioning may reduce body weight (-4–2%) as well as blood pressure (-8–3%); and b) inconsistent findings and limited understanding still exist for determining the impact of acute and chronic hypoxic conditioning on markers such as triglycerides, cholesterol levels and fitness capacity. Also, published findings, at present, do not clearly show changes in responses of HR, fat and muscle mass following hypoxic conditioning being significantly larger than a matched exposure and/or exercise period in normoxic conditions. Nevertheless, the promising findings need larger cohorts, assessment of exercise-related sensations and cognitive function, and real-world applications of findings to support and develop the current literature regarding hypoxic conditioning for obese populations. Novel training interventions such as shorter training periods (two weeks for example) that have been shown to induce similar cardio-metabolic health benefits to longer training periods (≥four weeks) should be implemented to further investigate the potential effectiveness of this. Finally, utilisation of a perceptually-regulated exercise intensity during active hypoxic conditioning may be more appropriate for obese individuals to enjoy and adhere to exercise compared to a fixed-intensity, but this is unknown at present.

### 2.7. Research questions arising from the literature review

Following the review of literature regarding hypoxic conditioning for improving psycho-physiological responses in obese populations, the following questions arise as presented in figure 2.4.

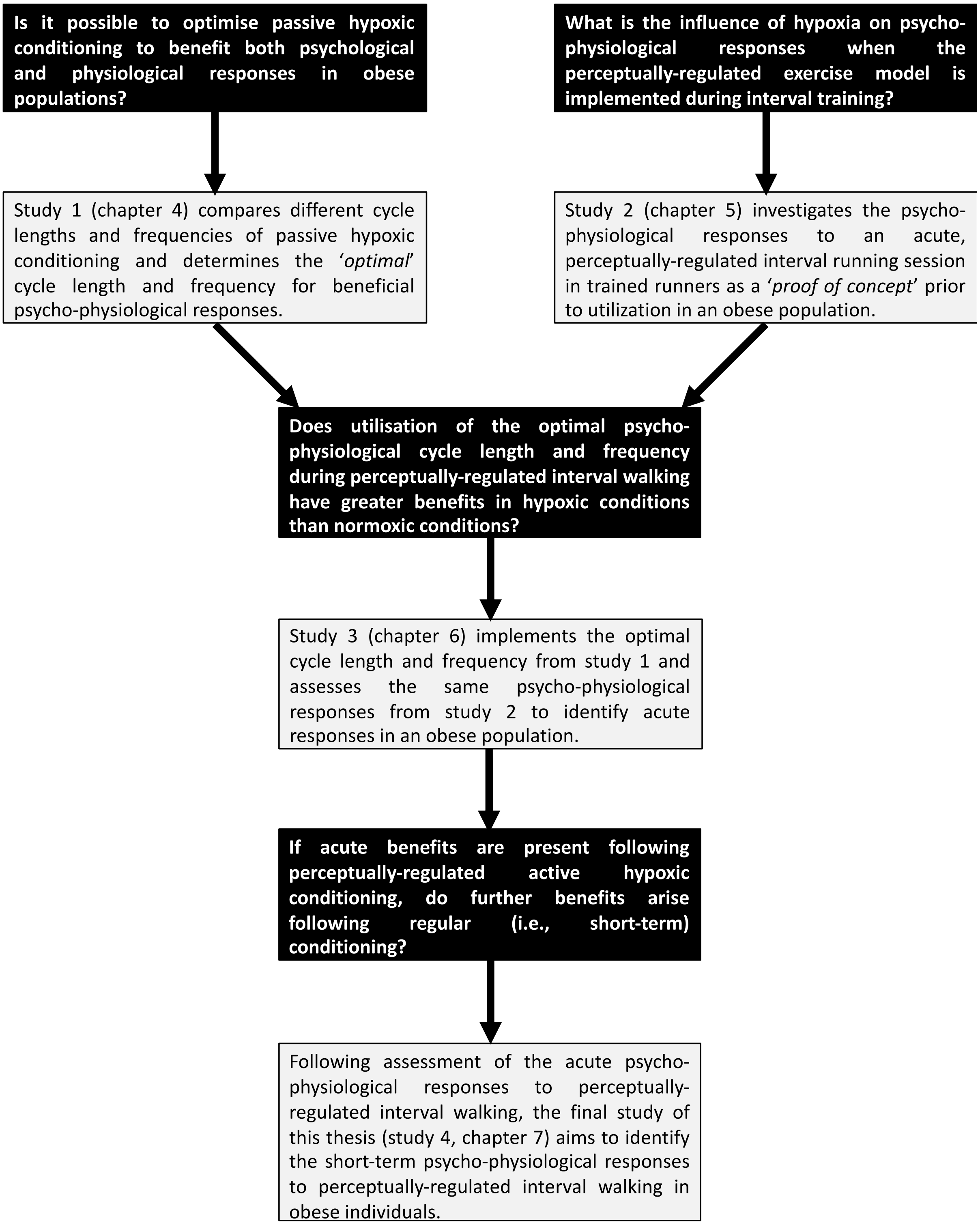


**Figure 2.4.** Overview of the research questions (black boxes) developed from the current literature review, and how the experimental studies within this thesis (light grey boxes) will answer these questions and relation between each other.

# 3. General methodology

This chapter details the common methodologies employed during the experimental trials carried out in the completion of this thesis. General information regarding exercise protocols, environmental conditions, procedures, techniques, and analysis are given. Additional information relating directly to individual studies are provided within each chapter where necessary. Study 1, 3 and 4 were conducted at London South Bank University (LSBU), whilst study 2 was carried out at the Sports Science Laboratory, Aspetar Orthopaedic and Sports Medicine Hospital, Qatar.

## 3.1. Ethics

Ethical approval for experimental studies was obtained from the dedicated ethics committee (School of Applied Science, LSBU; Anti-Doping Laboratory Qatar, Aspetar). The following registration codes were received from the ethics committee's per study; study 1: SAS1705, study 2: SCH-ADL-170, study 3: SAS1725, and study 4: SAS1822. Reference and adherence to the Declaration of Helsinki (2013) and laboratory standard operating procedures were also made.

## 3.2. Laboratory environments

Laboratory environments were maintained at a neutral air temperature (~23 °C) and humidity (~50%).

## 3.3. Participants

### *3.3.1. Recruitment*

Volunteers were recruited for each study *via* expression of interest in response to a recruitment advertisement poster posted online (social media channels) and on campus, and through word-of-mouth.

### *3.3.2. Eligibility*

Volunteers received a participant information sheet containing details of the study so they could make an informed decision regarding participation. If they decided to participate and subject to fitting the eligibility criteria outlined below, a familiarisation session was arranged in the laboratory. Eligible volunteers provided written informed consent prior to enrolling as a participant. Participants were advised that they could withdraw from a study at any point without providing a reason, and there would be no negative implications in doing so.

Please note that [1] denotes studies 1, 3 and 4 only (chapters 4, 6 and 7) and [2] refers to study 2 only (chapter 5).

Inclusion criteria were as follows:

- being aged between 18–55 years,
- having a BMI between 27–35 kg/m$^2$ (overweight & class I obese)[1],
- being sedentary (less than one hour of moderate intensity exercise per week) (van der Ploeg & Hillsdon, 2017)[1],
- a weekly running training volume of ≥6 h for the last two years[2],
- being free of clinical signs of disease, orthopaedic, neurological, degenerative, cardiovascular, respiratory or cognitive problems.

Exclusion criteria were as follows:

- a history of chest pain or shortness of breath, thrombosis, hypertension, anxiety, severe hearing loss or speech disorder,

- musculoskeletal injuries and/or abuse of drugs, medicine or alcohol,
- enrolled onto an instructed exercise/diet intervention to manage/reduce weight or other co-factors by a nutritionist/personal trainer[1],
- acclimatisation or exposure to hypoxia of more than 2500 m for more than 48 h during a period of 6 months before the study or a history of altitude-related sickness and health risk that could compromise the participant's safety during training and/or hypoxia exposure,
- a history of smoking, influenza, colds or urinary tract infections within six months prior to the start of the study,
- completion of ≥60 min physical activity (including any period of movement above a leisurely pace) each week[1],
- medication required for the treatment of migraines, claustrophobia or chronic back pain that may interfere with the interpretation of the results.

For calculation of BMI, height and weight were measured during using an electronic stadiometer (220, Seca GmbH, USA). Participants stood on a flat plated surface with their head in the Frankfort plane and their arms resting by their sides. They were instructed to take one deep breath after which a measurement of height was made. Body mass (kg) was displayed digitally on the scale monitor. The following calculation was used to determine BMI:

**BMI** (kg/$m^2$)

$$\text{body mass (kg)} / \text{height}^2 \text{ (m)}$$

(Khosla & Lowe, 1967)

Naturally, BMI does not take into account differences in lean and fat mass within the overall total body mass. However, where eligible volunteers were recruited within a particular BMI range for studies 1, 3 and 4 (chapters 4, 6 and 7) who were sedentary, it is unlikely that large quantities of muscle mass led to a BMI considered to be overweight or obese. Further, BMI assessment is considered as a highly specific measure for determining obesity (Adab et al., 2018) and is well correlated with other types of assessments for determining cardio-metabolic risks, such as waist circumference and waist: hip ratio (Wormser et al., 2011).

### 3.4. Familiarisation procedures

Each experimental study included a familiarisation session. Volunteers received explanations and demonstrations of all equipment and procedures, as well as being familiarised with specialist equipment and measurement tools (i.e., treadmill running/walking, perceptual scales, cognitive testing). For studies 2, 3 and 4 (chapters 5, 6 and 7), participants' self-selected exercise intensity was also determined. This session permitted volunteers to ask questions regarding the study demands and requirements, which were answered by the investigator.

### 3.5. Experimental trial standardisation

Prior to every trial across the experimental studies, participants attended the laboratory after refraining from caffeine, alcohol and vigorous exercise for ≥48 h. This was to minimise the impact of these factors on psycho-physiological responses assessed within the experimental studies. Where venepuncture was carried out in studies 1, 3 and 4 (chapters 4, 6 and 7), participants arrived at the laboratory 12 h post-prandial (Matu et al., 2017). Participants completed all experimental trials at a similar time of day to prevent the impact of circadian rhythm variation on measured parameters (Carrier & Monk, 2000). Whilst enrolled onto the study, participants were asked to maintain their habitual daily routine of diet, sleep and exercise patterns.

### 3.6. Determination of self-selected exercise intensity

Experimental studies 2, 3 and 4 (chapters 5, 6 and 7) included the utilisation of a self-selected (i.e., perceptually-regulated) exercise intensity. This intensity was determined on a treadmill in normoxic conditions using a modified version of the validated method by Martin et al. (1992). The original method included a series of 5-min treadmill walking episodes ranging from 2.4–7.2 km/h whilst expired gas was collected, to describe the velocity-aerobic demand relationship between populations of different physical activity status and age during walking. Modification of the method involved shorter, repeated treadmill walking episodes to identify a preferred exercise intensity for interval training, determined by RPE and HR. Further modifications were made to the method for study 2 (chapter 5) to reflect running velocities (9–19.5 km/h) rather than walking in study 3 and 4 (chapters 6 and 7, 2.4–7.2 km/h). Participants completed four ramps (increasing and decreasing velocities) whilst ambulating on the treadmill. After every 20 s during each stage, HR was recorded and participants were asked to rate their RPE of the current velocity (velocity was controlled by the investigator and blinded to the participant) in accordance with the previously validated 6–20 numeric scale (Borg et al., 1987). The ramps were as follows:

1. increasing velocity by 0.8 km/h until RPE ≥18,
2. decreasing velocity by 0.8 km/h $^{\text{from}}$ +1.5 km/h faster than the previous end velocity until RPE ≤9,
3. increasing velocity by 0.5 km/h from previous velocity rated as RPE = 12 in ramp two until RPE ≥18, and
4. decreasing velocity 0.5 km/h from +1.0 km/h faster than the previous end velocity until RPE ≤9.

In study 2 (chapter 5), ramp one started at 10.0 km/h, and studies 3 and 4 (chapters 6 and 7) began at 2.4 km/h. This was due to the differentiation between self-selected running and walking velocity, respectively. A ramp was terminated if participants could not maintain the current velocity (studies 2–4, chapters 5–7) or if they had to break into a jog/run (studies 3 and 4, chapter 6 and 7). Each ramp began once the participants declared their perceived recovery level ≥7 out of 10 ("*well recovered*") following the previous ramp (Laurent et al., 2011). Self-selected running velocity corresponded to the velocity participants considered as an RPE of 16 (between "*hard*" and "*very hard*") or closest to a HR of 160 bpm (study 2, chapter 5). Self-selected walking velocity corresponded to the velocity participants considered as an RPE of 14 (between "*somewhat hard*" and "*hard*") or closest to a HR of 140 bpm (studies 3 and 4, chapter 6 and 7).

### 3.7. Exercise sessions

In studies 2, 3 and 4 (chapters, 5, 6 and 7), participants carried out interval running/walking on a motorised treadmill (see specific chapters for models). Each session began with a standardised 5-min warm up at 10 (study 2, chapter 5) or 3 km/h (studies 3 and 4, chapters 6 and 7). Participants rested for 1-min (quiet standing) before initiating the first of four 4-min (study 2, chapter 5) or 15 2-min (studies 3 and 4, chapters 6 and 7) intervals. The first 30 s of each interval began at participants' self-selected intensity. Participants were then free to decide if/how the treadmill velocity needed to be adjusted every 30 s (manually by one investigator) to ensure maintenance of the target RPE. Participants firstly hand-signalled in response to the current velocity (finger up to increase, finger down to decrease, and circle using finger and thumb to maintain); and signalled secondly to inform how much of an increase/decrease in velocity is required [1, 2 or 3 fingers up (faster) or down (slower) for 0.5, 1.0 or 1.5 km/h changes, respectively]. Signals were trialled during the familiarisation session. Mild verbal encouragement and reminders of the target RPE were used throughout interval training. Participants remained on the treadmill (standing quietly) during the recovery periods between intervals. Measures that may have impacted pacing during exercise (i.e., treadmill velocity, HR and $SpO_2$) were positioned outside of the participants viewing area.

The inclusion of a self-selected exercise intensity over conventional percentages of $HR_{MAX}$ or $VO2_{MAX}$ were made for multiple reasons. Firstly, interval training in hypoxic conditions at matched, absolute, fixed exercise intensities leads to over-induced physiological stress due to a compensatory increase in HR compared to normoxic conditions (Heinonen et al., 2016). Secondly, exercising at a self-selected pace generates larger positive affective responses in healthy (Parfitt et al., 2000) and non-healthy (Parfitt et al., 2006) populations compared with a prescribed intensity. And finally, imposing an exercise intensity that is just 10% greater than a self-selected intensity decreases sensations of pleasure in overweight individuals (Ekkekakis & Lind, 2006).

### 3.8. Hypoxic conditioning

Participants wore a facemask connected *via* corrugated plastic tubing to a hypoxic generator (study 1, 3 and 4: Everest Training Summit II, Hypoxico Altitude Training Systems, USA; study 2: AltiTrainer, SMTec SA, Switzerland) for hypoxic conditioning (Figure 3.1.). The hypoxic generator enriches the air expired from the system with nitrogen, subsequently lowering the $FiO_2$, which is manually controlled with digital adjusters on the generator, fed to the participant. Reservoir bags were placed along the corrugated tubing to minimise the positive pressure of air flow. An oxygen analyser (GA-200 CO2 and O2 Gas Analyzer, iworx, USA) continuously assessed the $FiO_2$ to ensure the accuracy of the hypoxic stimulus during each trial. One hypoxic generator was used by each participant at a given time.

To ensure blindness of the environmental condition, the hypoxic generator was hidden from the participants view. Additionally, when breathing ‘normal air’ during normoxic conditions or the control trials, the hypoxic generator was set at a simulated altitude of 100 m (i.e., the machine remained switched on at sea level conditions) to increase the strength of blinding of the intervention. Where necessary, it was possible to turn the hypoxic generator off and allow participants to breathe room air *via* removal of the mask from the face in an emergency (i.e., $SpO_2$ <75%, $FiO_2$ <8%, or verbal/visual discomfort displayed by the participant).

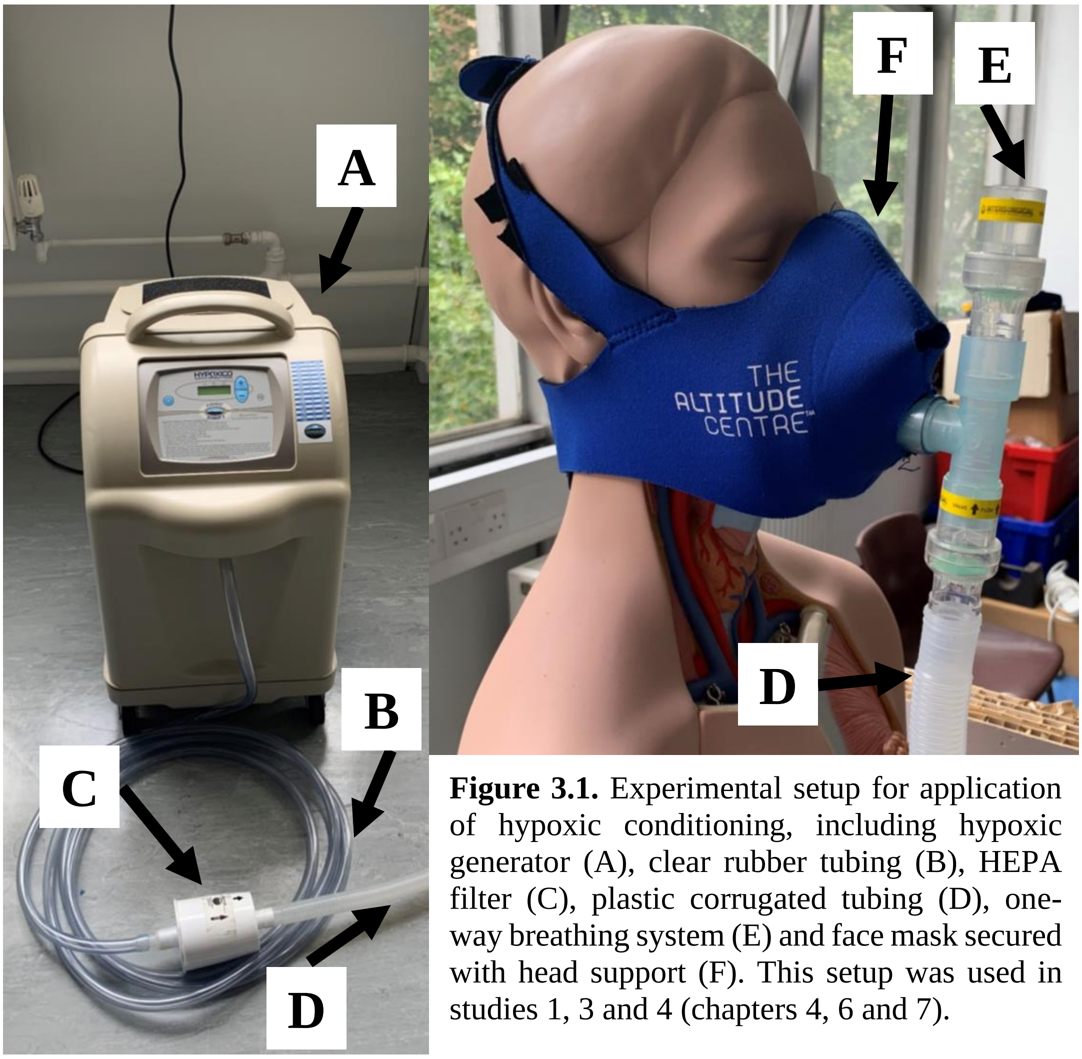


**Figure 3.1.** Experimental setup for application of hypoxic conditioning, including hypoxic generator (A), clear rubber tubing (B), HEPA filter (C), plastic corrugated tubing (D), one-way breathing system (E) and face mask secured with head support (F). This setup was used in studies 1, 3 and 4 (chapters 4, 6 and 7).

## 3.9. Physiological responses

### *3.9.1. Heart rate*

HR was monitored telemetrically with a chest strap (H10, Polar, Finland) connected *via* Bluetooth to a watch (M400, Polar, Finland) and manually recorded every 30 s in studies 2, 3 and 4 (chapters 5, 6 and 7).

### *3.9.2. Arterial oxygen saturation*

$SpO_2$ was assessed *via* finger pulse oximetry (iHealth Air, iHealthLabs, USA) and recorded continuously (study 1; chapter 4) or manually every 30 s (studies 2–4; chapters 5–7).

### *3.9.3. Blood pressure*

Blood pressure was assessed at rest by attachment of a pressure cuff secured with Velcro around the participants' left upper arm. Automated inflation (to 170 mmHg) and deflation of the cuff occurred alongside assessment of pulse rate (Omron M4, Omron, Japan). Systolic and diastolic values were recorded manually. A single measurement was completed unless there was uncertainty in the values (due to measurement error) by the investigator (Beevers et al., 2001).

### *3.9.4. Near-infrared spectroscopy*

Muscle oxygenation trends were recorded (Spike2, CED, Cambridge) using near-infrared spectroscopy in real-time. Two systems were used across the experimental studies based on equipment availability across laboratories (study one and three: NIRO-2000NX, Hamamatsu, Japan; study two: Portalite, Artinis, Netherlands). For setup of both systems, bi-polar optode sensors were attached *via* double-sided adhesive tape and housed 3 cm apart within rubber-cased hoods. Individual wavelengths when recording peripheral musculature were selected based on the depth of adipose fat tissue assessed over the *vastus lateralis* using Doppler ultrasound sonography (Sonosite, Titan, USA) (Rupp et al., 2013). Sampling frequency was set at 10 Hz (Chacaroun et al., 2018) following a 'zero set' of all signals. Bandages were fastened around the area of interest and optode to prevent external light impacting on the signals. The following parameters, along with their calculation, were recorded *via* emission and absorption of near-infrared light to tissue in accordance with the modified Beer-Lambert law (Kocsis et al., 2006), and exported at 1 Hz:

**Oxygenated haemoglobin** (Δμmol) ($[O_2Hb]$)

$$= p^{(a)}\left(r_1^{(a)}\frac{\Delta PO_2{}^{(a)}}{PO_2{}^{(a)}}+\frac{\Delta V_{bv}^{(a)}}{V_{bv}^{(a)}}\right)+p^{(c)}\left[q_1{}^{(c)}\left(r_1^{(c)}\frac{\Delta PO_2|_0^{(c)}}{PO_2|_0^{(c)}}+\frac{\Delta V_{bv}^{(c)}}{V_{bv}^{(c)}}\right)\right.$$
$$\left.+q_2{}^{(c)}\left(-\frac{\Delta\alpha_{\dot{O}_2}}{\alpha_{\dot{O}_2}}+\frac{\Delta c^{(c)}}{c^{(c)}}\right)\right]+p^{(v)}\left(r_1^{(v)}\frac{\Delta PO_2{}^{(v)}}{PO_2{}^{(v)}}+\frac{\Delta V_{bv}^{(v)}}{V_{bv}^{(v)}}\right)$$

**Deoxygenated haemoglobin** (Δμmol) ([HHb])

$$= p^{(a)}\left(-r_1^{(a)}\frac{\Delta PO_2{}^{(a)}}{PO_2{}^{(a)}}+r_2{}^{(a)}\frac{\Delta V_{bv}^{(a)}}{V_{bv}^{(a)}}\right)+p^{(c)}\left[-q_1{}^{(c)}r_1^{(c)}\frac{\Delta PO_2|_0^{(c)}}{PO_2|_0^{(c)}}\right.$$
$$\left.+r_2{}^{(c)}\left(q_1{}^{(c)}\right)\frac{\Delta V_{bv}^{(c)}}{V_{bv}^{(c)}}-q_2{}^{(c)}\left(-\frac{\Delta\alpha_{\dot{O}_2}}{\alpha_{\dot{O}_2}}+\frac{\Delta c^{(c)}}{c^{(c)}}\right)\right]$$
$$+p^{(v)}\left(-r_1^{(v)}\frac{\Delta PO_2{}^{(v)}}{PO_2{}^{(v)}}+r_2{}^{(v)}\frac{\Delta V_{bv}^{(v)}}{V_{bv}^{(v)}}\right),$$

(Watanabe et al., 2017)

where $PO_2^{(i)}$, $V^{(i)}$, $\alpha_{O2}$ and $c^{(c)}$ are variables describing partial pressure of oxygen, partial blood volume, oxygen utilization rate, and the speed of blood flow, respectively. $\Delta[O_2Hb]$ and Δ[HHb] are expressed by summation of normalized changes $\Delta PO_2^{(i)}$ (i = a, c, and v), $\Delta V^{(i)}$ (i = a, c, and v), $\Delta\alpha_{O2}$, and $\Delta c^{(c)}$ with coefficients $p^{(i)}$, $q1^{(c)}$, $q2^{(c)}$, $r1^{(i)}$, and $r_2^{(i)}$ (i = a, c, and v).

**Total haemoglobin** (μΔμmol) ([tHb])

$[O_2Hb]$ + [HHb]

(Rupp et al., 2013)

**Tissue oxygenation** (%) (TSI)

$$TOI = SaO_2 - \left(\frac{V_v}{V_a+V_v}\right)\cdot\left(\frac{CMRO_2}{k.CBF.[Hb]}\right)\times 100$$

(Tisdall et al., 2009)

where, $SaO_2$ = arterial oxyhemoglobin saturation, $V_V$ and $V_a$= venous and arterial blood volume, respectively, $CMRO_2$, cerebral metabolic rate for oxygen, k = oxygen carrying ability of hemoglobin, CBF = cerebral blood flow and [Hb] = blood Hb concentration.

As described in detail by Rupp et al. (2013), NIR-determined hemodynamics reflect the dynamic balance between oxygen demand and supply, and have been validated when assessing human reponses to hypoxic conditioning.

## 3.10. Metabolic responses

### *3.10.1. Breath-by-breath expired gas*

An opto-electric turbine flow meter connected to a metabolic cart (Quark CPET™, Cosmed, Italy) measured 5-min breath-by-breath expired gas samples. This procedure and duration of measurement has been validated previously to assess resting expired gas responses (Isbell et al., 1991). After warming up for 15 mins and before use, manual calibration of environmental gas volumes and concentrations were completed in normoxic conditions according to the manufacturer guidelines. A silicone Hans Rudolph facemask secured over participants' mouth and nose *via* a Velcro head strap permitted monitoring of pulmonary gas exchange. Measurements were recorded using an online gas analysis program (PFT Ergo, Cosmed, Italy) as previously validated (Nieman et al., 2013). Calculations of metabolic responses *via* expired gas samples presented within this thesis are found below:

**Minute ventilation** (L/min)

$$\text{Breathing frequency} \times \text{tidal volume}$$

**Oxygen uptake** ($VO_2$) (L/min)

$$[V_I \times FiO_2] - [V_E \times FeO_2]$$

**Carbon dioxide output** ($VCO_2$) (L/min)

$$[V_E \times FeCO_2] - [V_I \times F_ICO_2]$$

Haldane transformation (Wilmore & Costill, 1973)

Where $V_I$ is total volume inspired, $V_E$ is total volume expired, $FeO_2$ is the fraction of expired oxygen, $FeCO_2$ is the fraction of expired carbon dioxide, and $F_ICO_2$ is the fraction of inspired carbon dioxide.

**EE** (kcal/min)

$$[3.94 \times VO_2] + [1.11 \times VCO_2]$$

(Weir, 1949)

**Respiratory exchange ratio** (RER)

$$VCO_2 / VO_2$$

**Fat metabolism** (g/min)

$$[1.695 \times VO_2] – [1.701 \times VCO_2]$$

**Carbohydrate metabolism** (g/min)

$$[4.59 \times VO_2] – [3.23 \times VCO_2]$$

(Lusk, 1923)

The non-invasive and advantageous nature of using indirect calorimetry to assess fat and carbohydrate metabolism in humans is well reviewed by Ferrannini (1988). This technique has also previously been carried out following passive (Workman & Basset, 2012) and active (Kelly & Basset, 2017) hypoxic conditioning.

### *3.10.2. Blood lactate and glucose concentrations*

After cleaning of the fingertip with an alcohol swab (IPA Swab, Medisave, UK) and then leaving to dry naturally, a single-use lancet (Accu-Chek Safe-T Pro Plus, Roche, USA) was used to draw a small (~0.9 µl) capillary blood sample. Initial blood was wiped away to remove risk of contamination of tissue with fluid and debris (WHO, 2010), with the fingertip gently '*milked*' to collect a sample. Samples were dropped onto a test strip and analysed immediately for blood lactate ($[La^+]$) (Lactate Pro, Arkray, Japan) in study 2 (chapter 4) or glucose concentrations (Glucometer, Medisave, UK) in studies 3 and 4 (chapters 6 and 7). Following sampling, the bleeding site was compressed with fluid absorbable tissue until bleeding ceased. Test strips and lancets were disposed of following standard procedures immediately after analysis.

## 3.11. Perceptual responses

### *3.11.1. Recovery*

Perceived recovery was assessed by participants answering ‘*how recovered do you feel currently?*’ *via* a numeric scale, ranging from 0 being ‘*very poorly recovered*’ to 10 being ‘*very well recovered*’ (Laurent et al., 2010) (appendix 1).

### *3.11.2. Motivation*

Perceived motivation to exercise was assessed *via* a 20 cm visual analog scale (Crewther et al., 2016) (appendix 2). Participants were asked ‘*how motivated do you feel to exercise right now?*’ to which they answered by adjusting the level on the scale between 0 being ‘*not very motivated*’ (white colored) and 20 being ‘*very motivated*’ (black colored).

### *3.11.3. Breathlessness*

Perceived breathlessness was assessed by answering ‘*how does your breathing feel currently?*’ *via* a numeric scale (appendix 3), ranging from 0 being ‘*nothing at all*’ to 10 being ‘*very, very severe*’ (Ward & Whipp, 1989).

### *3.11.4. Limb discomfort*

Using the same scale for perceived breathlessness, perceived limb discomfort was assessed by the investigator asking the participant ‘*how do your legs feel currently?*’ (appendix 4).

### *3.11.5. Pleasure*

A 20 cm visual analog scale (same as the scale used for motivation above) was used to assess '*how pleasant was that run?*' ranging from 0 being '*not very pleasant*' and 20 being '*very pleasant*' (appendix 5).

### *3.11.6. Mood state*

Participants were asked '*how are you feeling right now?'* and instructed to verbally specify a number on an 11-point scale anchored '*very bad*' (-5) up to '*very good*' (+5) for perceived mood state (Hardy & Rejeski, 1989) (appendix 6).

### *3.11.7. Positive and negative affects schedule*

Positive and negative affects (PANAS) were assessed *via* a 20-item 5-point Likert scale. Participants were instructed to answer how they feel towards 20 emotions including '*interested'*, '*distressed'* and '*excited'*, ranging from '*very slightly or not at all*' (1) to '*extremely*' (5). Items were totaled for positive and negative responses (Watson & Clark, 1988) (appendix 7).

### *3.11.8. Exercise self-efficacy*

Exercise self-efficacy was assessed *via* a six item 11-point Likert scale. Participants were instructed to answer how confident they feel in '*carrying out exercise 3 times per week at a moderate-intensity for 40+ minutes without quitting*' for 1–6 months from '*not at all confident*' (0) up to '*highly confident*' (Smith et al., 2012) (appendix 8). This Likert scale was in reference to exercise generally, and not the exercise employed in this thesis.

## **3.12. Cognitive function**

Cognitive function was assessed during rest, in a silent normoxic environment without audible or visual distractions in studies 2, 3 and 4 (chapters 5, 6 and 7). Two different offline, computerised cognitive tests were employed, due to differences in the population of interest per study (healthy, trained runners *versus* obese individuals).

### *3.12.1. Stroop colour-word test*

A Stroop colour-word test (Stroop, 1935) assessed attention and executive function of healthy, trained runners. This test lasted for three minutes, whereby individual stimuli were repeatedly displayed on the screen for 500 ms. Participants selected a labelled key on the keyboard (x, v, n, or <) representing the color of the text appearing on the screen (red, yellow, green or blue, respectively).

### *3.12.2. n-back task*

An *n*-back task (Braver et al., 1997) assessed working memory of obese individuals. This included 30 *0*-back trials and 30 *1*-back trials randomly arranged. For each trial, a single neutral image (i.e., a cat) was displayed for 500 ms. Participants were required to respond to the image by selecting one key (i.e., number one) if the image displayed matched the target stimuli, or a separate key (i.e., number two) if the image displayed did not match the target (i.e., non-target) stimuli. For 0-back, the target stimuli were presented at the start of the task (same image throughout 30 trials).

During both cognitive tests, participants were instructed to respond to each stimulus as quickly as possible using one hand, with their other tucked behind their back. Accuracy (number of correct responses; %) and reaction time (to respond; ms) were averaged across each cognitive test and recorded as an indication of performance.

## 3.13. Functional fitness

Functional fitness was determined *via* a 6-min walk test (Gibson et al., 2014) in study 4 (chapter 7). Briefly, participants stepped onto the treadmill belt at 50% of their self-selected walking velocity. Within ~10 s, the treadmill velocity was increased to 100% of their self-selected walking velocity and the 6-min duration began. Participants were instructed to "*walk as far as possible in six minutes without running or jogging*" and were able to adjust the velocity where necessary as described in the "*Exercise sessions*" section of this chapter to achieve the farthest distance. Velocity was monitored every 30 s, and the total distance covered in the 6 mins was recorded. This test for assessment of functional fitness was selected as a more practical and applicable method compared to previously used assessments (i.e., $VO2_{MAX}$/$VO2_{PEAK}$) in overweight and obese individuals (Hobbins et al., 2017).

### 3.14. Data processing

Procedures for data processing are detailed within each experimental study chapter.

### 3.15. Statistical analysis

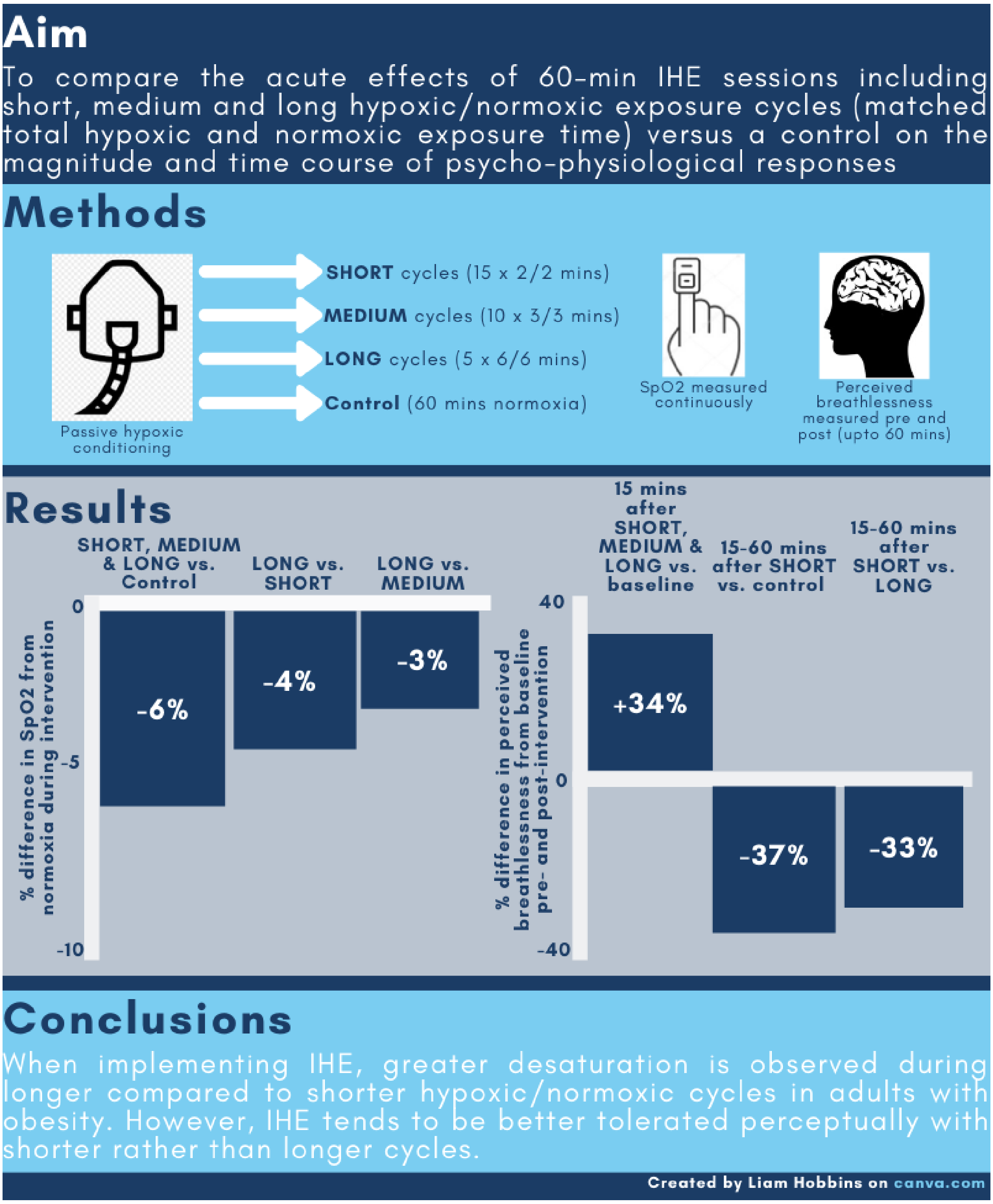
Power analyses were carried out prior to data collection to determine appropriate sample sizes for each experimental study (G*Power 2, HHU, Germany). The guidelines for determining $\alpha$ priori were adhered to (Prajapati et al., 2010), with $\alpha$ (0.05) and $\beta$ (0.8) values accordingly set. Using pilot testing data, subsequent analysis revealed that 12 participants for study 1, 2 and 3 (chapters 4, 5 and 6) and 14 participants (per group) for study 4 (chapter 7) were needed to meet the required power.

Data distribution was assessed *via* a Shapiro-Wilk normality test. If data were normally distributed, a parametric within-subject analysis of variance (ANOVA), aligned with a Sidak confidence interval adjustment, was used to investigate the main effect of condition, time and the condition × time interaction. Sphericity was assessed *via* a Mauchly test, to consider that variations of differences are equal (Field, 2013). If sphericity was violated, a Greenhouse

Geisser correction was applied. Partial eta-squared was calculated as an estimation of effect size (ES). Values of 0.01, 0.06 and above 0.14 were considered as small, medium and large, respectively (Cohen, 2013). If data were not normally distributed, a related-samples non-parametric Friedman's test was used. If any significant effects were found, further post-hoc analysis was carried out *via* Bonferroni pairwise comparisons to assess where the significance lay. Statistical testing was carried out in SPSS (v21, IBM, Cambridge). All data are presented as mean ± standard deviation (SD), and considered statistically significant if $p \leq 0.05$ and a trend for significance if $p \leq 0.07$.

# 4. Acute psycho-physiological responses to cyclical variation of intermittent hypoxic exposure in adults with obesity

## 4.1. Graphical abstract



**Aim**

To compare the acute effects of 60-min IHE sessions including short, medium and long hypoxic/normoxic exposure cycles (matched total hypoxic and normoxic exposure time) versus a control on the magnitude and time course of psycho-physiological responses

**Methods**

Passive hypoxic conditioning

**SHORT** cycles (15 x 2/2 mins)

**MEDIUM** cycles (10 x 3/3 mins)

**LONG** cycles (5 x 6/6 mins)

**Control** (60 mins normoxia)

SpO2 measured continuously

Perceived breathlessness measured pre and post (upto 60 mins)

**Results**

**Conclusions**

When implementing IHE, greater desaturation is observed during longer compared to shorter hypoxic/normoxic cycles in adults with obesity. However, IHE tends to be better tolerated perceptually with shorter rather than longer cycles.

Created by Liam Hobbins on canva.com

## 4.2. Abstract

**Aim** Comparison of acute psycho-physiological responses to a single intermittent hypoxic/normoxic exposure (IHE) trial with varying cycle lengths in adults with obesity.

**Methods** Eight obese adults (BMI = 33.0 ± 2.2 kg/m$^2$) completed three 60-min IHE trials (passive seating), separated by seven days. Trials comprised 30-min hypoxia/30-min normoxia ($FiO_2$ = 12.0%/20.9%) over Short (15 × 2/2 min), Medium (10 × 3/3 min) and Long (5 × 6/6 min) hypoxic/normoxic cycles, and a control trial (60-min normoxia).

**Results** $SpO_2$ was lower during hypoxic periods of Long *versus* Medium and Short trials (90.1% *versus* 93.0% and 94.2%; $p = 0.02$ and $p = 0.05$, respectively), with no differences between Short and Medium. Pre-frontal cortex oxygenation was lower (-5.1%) during all IHE interventions *versus* control ($p < 0.02$), independently of cycle length. Perceived breathlessness was unaffected during IHE, but increased 15-min after exposure *versus* baseline (+34%; $p = 0.04$). Breathlessness was lowest after Short *versus* control from 15–60-min (-7%; $p = 0.01$).

**Conclusions** When implementing IHE, greater desaturation is observed during longer compared to shorter hypoxic/normoxic cycles in adults with obesity. However, IHE tends to be better tolerated perceptually with shorter rather than longer cycles.

## 4.3. Introduction

Continuous passive exposure to hypoxia (3 h, clamped $SpO_2$ ~75%) increases energy expenditure compared to normoxia (Workman & Basset, 2012). In overweight and obese individuals, this positive finding may assist with promoting a negative energy balance, required for weight loss. However, continuous hypoxic exposure (several hours) *versus* normoxia may exacerbate sympathetic nervous system activity, raising the risk of elevated blood pressure, tachycardia and rate pressure product in 'at-risk' individuals (White et al., 1985).

Intermittent hypoxic exposure (IHE) includes cycles of hypoxia and normoxia lasting from a few minutes to hours (Urdampilleta et al., 2012). Decreased cerebral oxygenation and blood pressure, during and immediately after one ~1 h IHE session, were found in healthy and overweight individuals *versus* a normoxic baseline (Chacaroun et al., 2017; Costalat et al., 2017). Although positive physiological responses have been reported, the aforementioned studies utilised individually-tailored hypoxic intervals (~5-min) to reach a target $SpO_2$ (~75%), rather than replicable standardized hypoxic/normoxic cycles. Currently no consensus regarding best practice IHE (i.e., optimal cycle length and frequency) for maximising physiological responses primarily exists for implementation in adults with obesity.

Between 3–15 cycles per session of moderate hypoxia ($FiO_2$ = 9.0–16.0%) is suggested to reduce blood pressure and increase blood glucose tolerance (daily sessions over four weeks) (Navarrete-Opazo & Mitchell, 2014). Evidence coming from animal studies indicates that longer, less frequent cycles will induce higher physiological (i.e., tissue de-oxygenation) stress *versus* shorter, more frequent cycles (Almendros et al., 2014). However, this is currently unknown in regard to obese individuals completing IHE for beneficial psycho-physiological responses.

Perception is a necessary component for investigating behaviour changes towards health (Schutzer & Graves, 2004). Stavrou et al. (2018) reported impaired mood state (i.e., greater depression and tension) during a 21-day hypoxic bed rest ($FiO_2$ = 15.0%) *versus* normoxia. To date, there is a lack of data including perceptual measures during and following (~60 mins) IHE. A low level of enjoyment is commonly cited as a reason for low/non-adherence to lifestyle interventions (King et al., 1988). Therefore, it is relevant to assess perception during IHE and potential influences of different cycles. Although exercise-based, studies have found lower perceived exertion when $SpO_2$ is >94% during hypoxic exercise *versus* <94% (Romer & Dempsey, 2006; Khaosanit et al., 2018). For IHE, perhaps more frequent re-oxygenation phases during shorter *versus* longer hypoxic cycles will permit more positive perception as $SpO_2$ will likely increase during normoxic cycles (Urdampilleta et al., 2012).

The aim of this study was to therefore compare the acute effects of 60-min IHE sessions including short, medium and long hypoxic/normoxic exposure cycles (matched total hypoxic and normoxic exposure time) *versus* a control on the magnitude and time course of psycho-physiological responses. It was hypothesised that the physiological stimulus (i.e., tissue de-oxygenation) would be greater, yet with less favourable perceptual responses (i.e., perceived breathlessness), during longer *versus* shorter cycles, with medium being the 'optimal' trade-off.

## 4.4. Methods

### *4.4.1. Participants*

Eight obese (5 females, 3 males; age: 37.0 ± 11.1 years; height: 170 ± 1 cm; weight: 93.9 ± 8.7 kg; BMI: 33.0 ± 2.2 $kg/m^2$) individuals participated in this study after meeting the eligibility criteria and providing written informed consent. This study received ethical approval from the School of Applied Science, LSBU (SAS1705).

### *4.4.2. Experimental design*

Participants attended the lab on five separate visits. First, they were familiarised with the study, including procedures/measures involved, and eligibility was determined. Eligible participants returned on four occasions at a similar time of day for the main experimental trials, each separated by seven days to enable a washout period (Kelly & Basset, 2017). Each experimental trial included a 60-min passive intervention, three of which included 30-min hypoxia ($FiO_2$ = 12.0%) and 30-min normoxia, and one in continuous normoxia (control) completed in a randomised order. The cyclical interventions were a) 15 × 2/2 mins (SHORT), b) 10 × 3/3 mins (MEDIUM) and c) 5 × 6/6 mins (LONG) in hypoxia/normoxia. All trials included a 60-min post-intervention period (normoxia). Blood pressure and perceptual responses (perceived mood state, motivation to exercise, and PANAS) were measured before and after each intervention. Perceptual responses (perceived mood state, breathlessness and motivation to exercise) and tissue (arterial and brain) oxygenation were assessed during. Participants arrived at the lab following an 8-h fast but were permitted to consume water. Participants were asked to replicate their dietary intake for remaining trials after the first (24-h prior), and continue their habitual routine during their time spent enrolled on the study.

### *4.4.3. Familiarisation session*

Participants were initially familiarised with the perceptual scales and physiological measurements. A 5-min period of passively breathing hypoxia ($FiO_2$ = 12.0%) was completed to familiarise participants with the sensations of the gas and wearing a facemask.

### *4.4.4. Experimental trials*

Participants rested in a seated position for 10 mins to enable haemodynamic stabilization (Thijsen et al., 2011) before being fitted with an ‘intervention’ facemask which provided exposure to hypoxic/normoxic gas for 60-min. Figure 4.1. illustrates the intervention

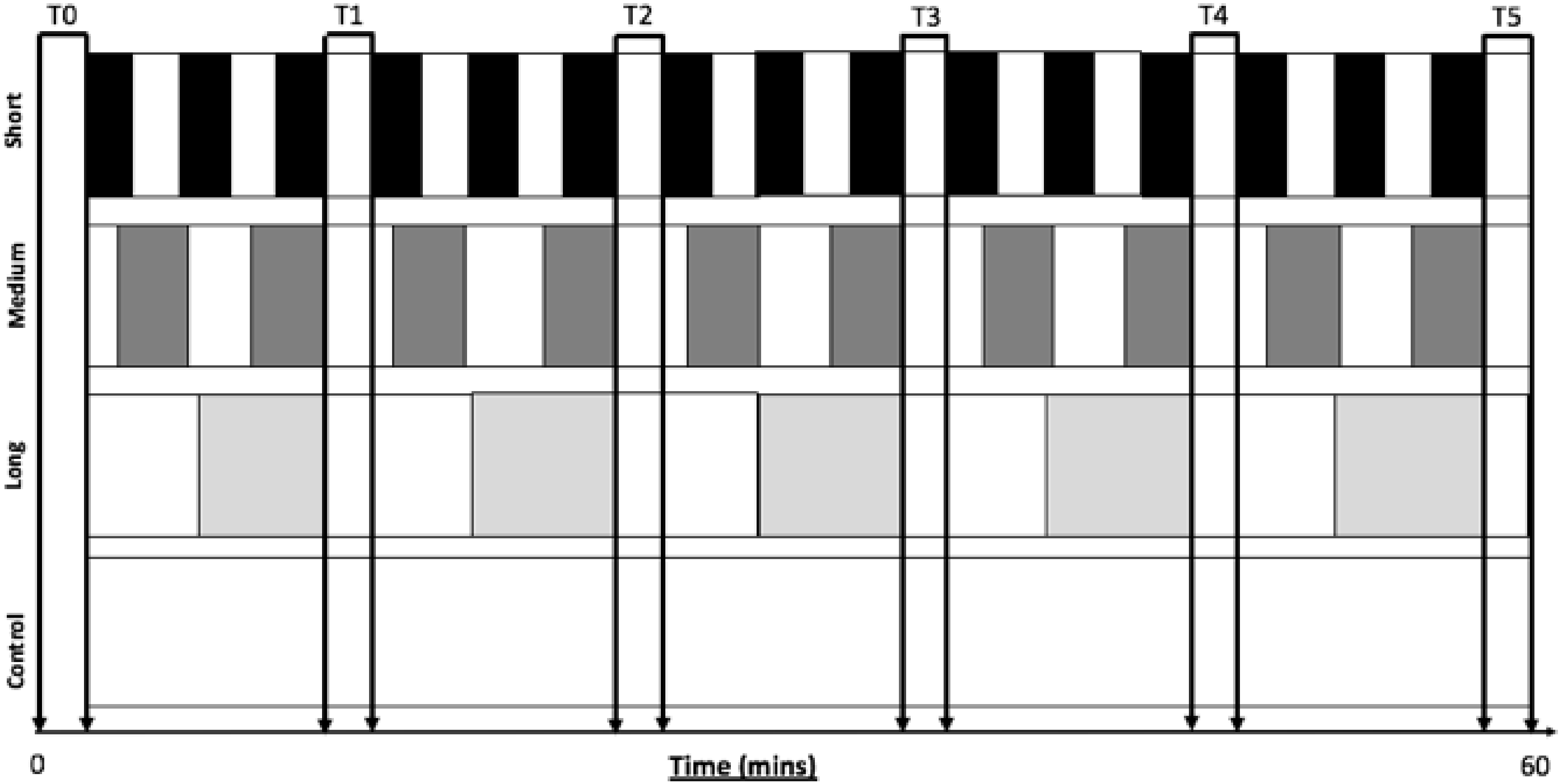


**Figure 4.1.** Overview of the 60-min intervention completed during each experimental trial. Participants were passively exposed to hypoxia (coloured bars) interspersed with exposure to normoxia (white bars). The time spent in hypoxia and normoxia per intervention was 30 mins, achieved *via* different cyclical variations: 15 × 2/2 (Short; black bars), 10 × 3/3 (Medium; dark grey bars) and 5 × 6/6 (Long; light grey bars) mins. An additional control trial involving continuous exposure to normoxia was also completed. Measurements were taken in normoxic conditions at 0 (T0), 10 (T1), 22 (T2), 34 (T3), 46 (T4) and 58 (T5) mins, as denoted by the arrows.

participants completed as part of each experimental trial. In a random order, participants completed 15 × 2/2 mins (SHORT), b) 10 × 3/3 mins (MEDIUM) and c) 5 × 6/6 mins (LONG) in hypoxia/normoxia, and 60 mins continuous normoxia (control). The 'intervention' facemask was removed after 60 mins for the following 60-min recovery period in normoxia. Entertainment (films/television programmes with similar neutral content across trials) was provided during the intervention.

### *4.4.5. Hypoxic conditioning*

Participants wore a facemask (Altitude Training Mask, Hypoxico Altitude Training Systems, USA) connected *via* corrugated plastic tubing to a hypoxic generator (Everest Training Summit II, Hypoxico Altitude Training Systems, USA) to create hypoxic conditions (3.8.). The $FiO_2$ provided in this study was 12.0% (simulated altitude of ~4500 m), deemed safe in the population studied (Navarrete-Opazo & Mitchell, 2014). An additional hypoxic generator was set at a 20.9% $FiO_2$ for normoxic cycles. A Hans Rudolph two-way valve positioned along the corrugated tubing permitted switching between gases. Participants' remained seated at all times during the intervention and instructed to maintain a normal breathing pattern by the investigator ("*breath as normally as you would without wearing a facemask*") prior to each trial. Total hypoxic exposure corresponded to exactly 30 mins during SHORT, MEDIUM and LONG.

### *4.4.6. Measures*

#### *4.4.6.1. During IHE*

$SpO_2$ (3.9.2.) and pre-frontal cortex oxygenation trends were recorded continuously using NIRS (NIRO-2000NX, Hamamatsu, Japan) in real-time (3.9.4.). Bi-polar optode sensors were attached over the left prefrontal cortex to illuminate the cortical area between standard Fp1 and F3 locations according to the international EEG 10-20 system (Chacaroun et al., 2017) *via* double-sided adhesive tape, and housed (3 cm apart, 775 Nm wavelength) within rubber-cased hoods. Perceived mood state (3.11.6.), breathlessness (3.11.3.) and motivation to exercise (3.11.2.) were assessed at 0 (T0), 10 (T1), 22 (T2), 34 (T3), 46 (T4) and 58 (T5) mins (corresponding to 0%, 20%, 40%, 60%, 80% and 100% of the 60-min intervention) in normoxia.

#### *4.4.6.2. Pre- and post-IHE*

Participants sat quietly during the recovery period. Blood pressure (3.9.3.) was assessed at baseline, and 15 (Post15), 30 (Post30) and 60 (Post60) mins after IHE.

Perceived mood state (3.11.6.), breathlessness (3.11.3.), motivation to exercise (3.11.2.) and PANAS (3.11.7.) were assessed at the same time points, immediately after assessment of blood pressure.

### *4.4.7. Data analysis*

Data were processed offline into Excel (Microsoft Office, 2016). $SpO_2$ data were averaged for time in hypoxia (30-min) and normoxia (30-min) for each IHE condition, and 60-min of normoxia for control. TSI data samples (2-min) were exported in hypoxia (before T1–T5) to compare an equal hypoxic duration between conditions at matched timepoints. Perceptual data were obtained in normoxic conditions to allow meaningful comparisons between IHE cycle variations and the control trial, all under normoxic conditions. TSI data were smoothed using a 5-point moving average and truncated *via* removal of the first and last 30-s of each 2-min (T0–T5) data collection period (1-min). TSI data were normalized by calculating percentage change from T0 (in normoxia) in each respective condition for statistical analysis, due to possible sensor placement differences. Perceptual data collected during the 60-min intervention and post-intervention periods were expressed as percentage change from T0 and baseline, respectively.

### *4.4.8. Statistical analysis*

A two-way ANOVA was used to investigate the main effect of condition (SHORT *versus* MEDIUM, LONG and control), time (baseline *versus* Post15, Post30 and Post60 or T0 *versus* T1, T2, T3, T4 and T5) and the condition × time interaction.

## 4.5. Results

### *4.5.1. During IHE*

$SpO_2$ was lower during SHORT, MEDIUM and LONG hypoxic *versus* normoxic cycles (-6%; $p < 0.001$, $F = 32.351$, ES = 0.822; Figure 4.2). Pairwise comparisons revealed $SpO_2$ during hypoxic LONG cycles were lower *versus* MEDIUM (-3%; $p = 0.023$) and SHORT (-4%; $p = 0.054$; Figure 4.2.).

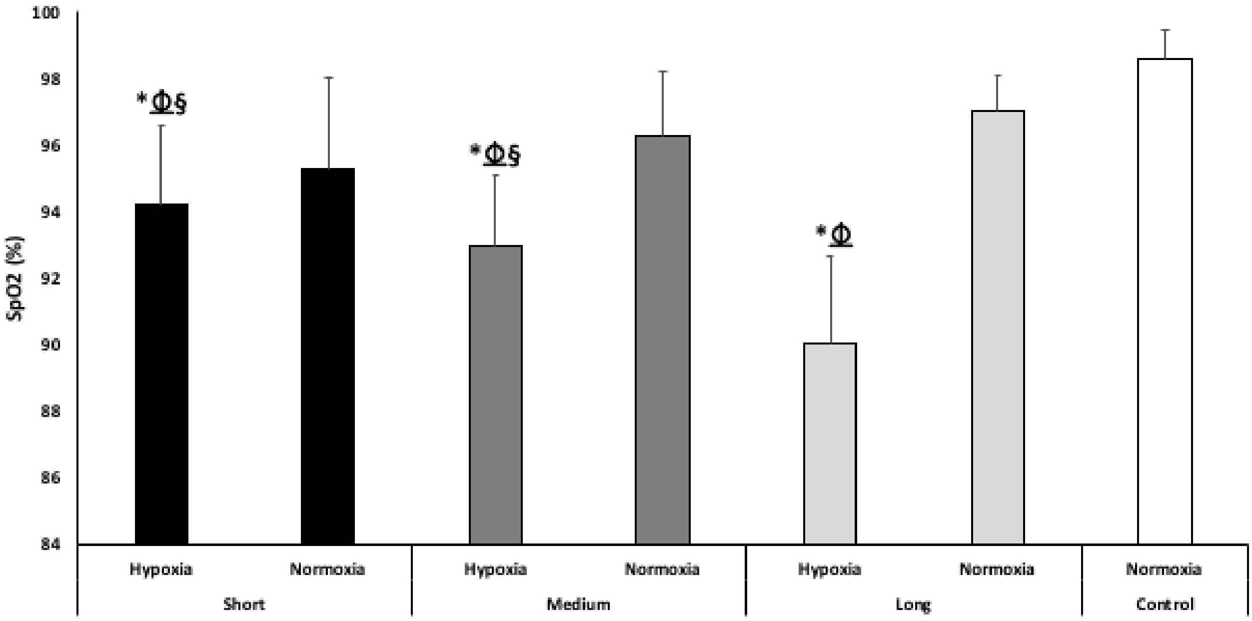


**Figure 4.2.** Arterial oxygen saturation ($SpO_2$) during the intervention. Values are presented as mean ± SD during hypoxic and normoxic periods (average of 30 min) for Short, Medium and Long, and average of 60 mins for control. Short = 15 × 2/2 mins; Medium = 10 × 3/3 mins; Long = 5 × 6/6 mins (hypoxia/normoxia). * denotes a statistically significant difference ($p < 0.01$) *versus* control; Φ denotes a statistically significant difference ($p = 0.03$) *versus* normoxia for a given condition; § denotes a statistically significant difference ($p = 0.05$) *versus* Long.

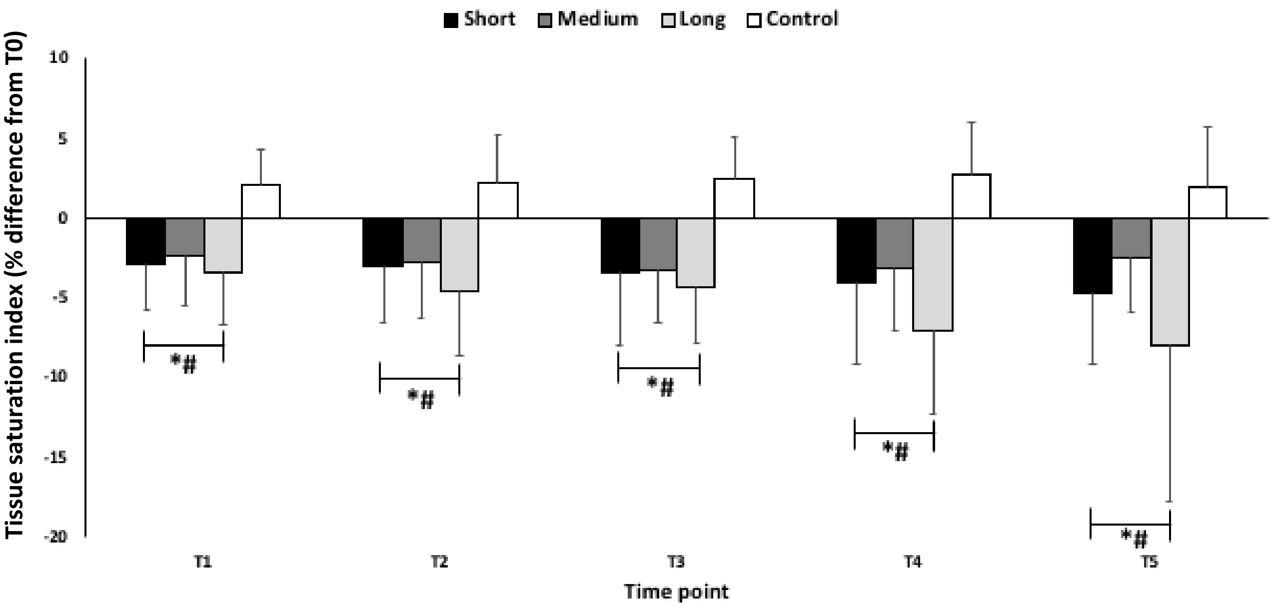


**Figure 4.3.** Tissue saturation index (TSI) data of the pre-frontal cortex measured during the intervention at 8 (T1), 20 (T2), 32 (T3), 44 (T4) and 56 (T5) mins in hypoxia during Short, Medium and Long cycles and in normoxia during control. T1 – T5 values are calculated as a percentage difference from T0 and are presented as mean ± SD. Short = 15 × 2/2 mins; Medium = 10 × 3/3 mins; Long = 5 × 6/6 mins (hypoxia/normoxia). * denotes a statistically significant difference ($p < 0.01$) *versus* control; # denotes a statistically significant difference ($p < 0.01$)

TSI decreased during SHORT (68.9 ± 3.6%), MEDIUM (69.1 ± 4.4%) and LONG (68.7 ± 5.3%) *versus* control (72.6 ± 4.9%; $p = 0.009$, $F = 8.237$, ES = 0.543; Figure 4.3). Compared to T0, TSI from T1–T5 were lower (-3%; $p = 0.011$; $F = 6.107$; ES = 0.543; Figure 4.3). There was no interaction effect on TSI ($p = 0.080$; $F = 2.997$; ES = 0.300).

No condition, time or interaction effects were observed for perceived mood, breathlessness and motivation to exercise during the 60-min intervention ($p \geq 0.05$; Table 4.1.).

*4.5.2. Pre- and post-IHE*

No condition, time or interaction effects existed for blood pressure ($p > 0.05$; Table 4.2).

There was a significant effect of condition ($p = 0.003$, $F = 6.617$, ES = 0.486) and time ($p = 0.001$, $F = 17.779$, ES = 0.717) but no interaction ($p = 0.146$, $F = 1.946$, ES = 0.218; Figure 4.4.a) on perceived breathlessness. Pairwise comparisons revealed perceived breathlessness greater 15 mins after the intervention *versus* baseline (+34%; $p = 0.040$; Figure 4.4a). Breathlessness during SHORT was lower *versus* control 15–60 mins after the intervention (*p*

= 0.001; Figure 4.4.a). Further, SHORT tended to be lower than LONG 15–60 mins after the intervention (*p* = 0.06). Positive affect decreased from 15–60 mins post-intervention *versus* baseline (*p* < 0.05), but was unaffected by condition (*p* > 0.05; Figure 4.4.b). Perceived mood state, motivation to exercise, negative affect and the ratio between positive and negative affect were unaffected by condition and did not change over time (*p* > 0.05; Table 4.2.).

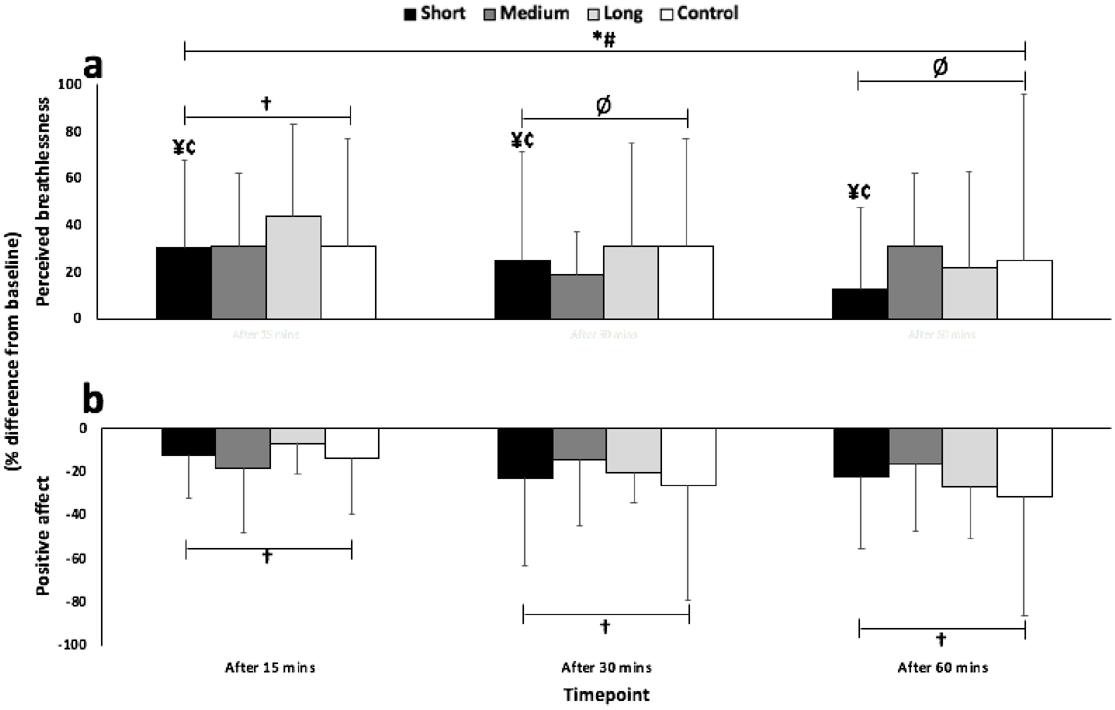


**Figure 4.4** Perceived breathlessness (a) and positive affect (b) data measured during the post-intervention period after 15, 30 and 60 mins. Values are calculated as a percentage difference from baseline and are presented as mean ± SD. Short = 15 × 2/2 mins; Medium = 10 × 3/3 mins; Long = 5 × 6/6 mins (hypoxia/normoxia). * denotes a statistically significant (*p* < 0.01) effect of condition; # denotes a statistically significant (*p* < 0.01) effect of time; † denotes a statistically significant (*p* < 0.01) difference *versus* baseline; Ø denotes a statistically significant (*p* < 0.02) difference *versus* 15 mins; ¥ denotes a statistically significant (*p* < 0.01) difference *versus* control; ¢ denotes a statistical trend (*p* < 0.06) difference *versus* Long.

**Table 4.1.** Perceptual measures recorded at 0 (T0), 10 (T1), 22 (T2), 34 (T3), 46 (T4) and 58 (T5) mins during Short, Medium and Long IHE interventions as well as the control trial.

| | | **Timepoint** | | | | | | **ANOVA *p* value (effect size)** | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Measure** | **Condition** | **T0** | **T1** | **T2** | **T3** | **T4** | **T5** | **Condition** | **Time** | **Interaction** |
| Mood state | Short | 4.13 ± 0.83 | 3.88 ± 1.13 | 3.75 ± 1.67 | 3.75 ± 1.75 | 3.38 ± 2.00 | 2.50 ± 2.00 | 0.584 (0.08) | 0.657 (0.08) | 0.727 (0.04) |
| | Medium | 3.63 ± 1.30 | 3.38 ± 1.69 | 3.63 ± 1.60 | 3.25 ± 2.19 | 3.50 ± 2.00 | 3.25 ± 1.98 | | | |
| | Long | 4.00 ± 1.20 | 3.63 ± 1.51 | 3.38 ± 1.85 | 3.13 ± 1.96 | 3.13 ± 2.10 | 2.75 ± 2.38 | | | |
| | Control | 3.13 ± 1.36 | 3.75 ± 1.04 | 3.25 ± 1.17 | 3.13 ± 1.64 | 3.13 ± 1.89 | 2.88 ± 2.03 | | | |
| Breathlessness | Short | 0.63 ± 1.03 | 1.19 ± 1.49 | 1.56 ± 1.88 | 1.31 ± 1.33 | 1.38 ± 1.41 | 1.19 ± 1.07 | 0.220 (0.21) | 0.101 (0.35) | 0.359 (0.14) |
| | Medium | 0.75 ± 1.16 | 1.06 ± 1.15 | 1.06 ± 1.47 | 1.13 ± 1.09 | 1.13 ± 1.46 | 1.06 ± 1.15 | | | |
| | Long | 0.63 ± 0.64 | 1.88 ± 1.25 | 1.81 ± 1.19 | 2.00 ± 1.85 | 1.94 ± 1.66 | 1.75 ± 1.67 | | | |
| | Control | 0.69 ± 0.88 | 1.00 ± 1.04 | 1.19 ± 1.07 | 1.31 ± 1.10 | 1.25 ± 1.39 | 1.13 ± 1.13 | | | |
| Motivation to exercise | Short | 12.63 ± 3.20 | 13.00 ± 2.73 | 12.88 ± 2.47 | 12.25 ± 3.58 | 12.75 ± 3.24 | 12.13 ± 3.36 | 0.435 (0.10) | 0.287 (0.16) | 0.351 (0.13) |
| | Medium | 12.50 ± 2.98 | 13.00 ± 2.93 | 12.63 ± 3.25 | 13.50 ± 3.63 | 13.75 ± 3.20 | 13.38 ± 3.66 | | | |
| | Long | 11.75 ± 5.12 | 10.88 ± 5.08 | 11.00 ± 5.78 | 11.25 ± 5.82 | 11.88 ± 5.87 | 11.50 ± 5.42 | | | |
| | Control | 12.13 ± 3.91 | 12.38 ± 3.29 | 13.25 ± 2.87 | 13.50 ± 2.88 | 13.50 ± 3.16 | 10.88 ± 3.91 | | | |

*Values are presented as group means* ± *SD.* Short = 15 × 2/2 mins; Medium = 10 × 3/3 mins; Long = 5 × 6/6 mins (hypoxia/normoxia).

SD, standard deviation; ANOVA, analysis of variance.

**Table 4.2.** Physiological and perceptual measures recorded at baseline and 15, 30 and 60 mins post-intervention during Short, Medium and Long IHE interventions as well as the control trial.

| | | **Timepoint** | | | | **ANOVA *p* value (effect size)** | | |
|---|---|---|---|---|---|---|---|---|
| **Measure** | **Condition** | **Baseline** | **+15 mins** | **+30 mins** | **+60 mins** | **Condition** | **Time** | **Interaction** |
| Systolic blood pressure (mmHg) | Short | 113.38 ± 10.97 | 108.63 ± 13.35 | 117.75 ± 12.21 | 113.75 ± 17.09 | 0.075 (0.27) | 0.661 (0.07) | 0.392 (0.13) |
| | Medium | 112.00 ± 15.36 | 116.57 ± 21.93 | 112.13 ± 13.58 | 110.50 ± 14.99 | | | |
| | Long | 116.14 ± 12.73 | 116.38 ± 16.05 | 122.25 ± 15.71 | 121.43 ± 12.51 | | | |
| | Control | 112.43 ± 17.55 | 115.86 ± 15.60 | 114.14 ± 13.03 | 114.00 ± 14.47 | | | |
| Diastolic blood pressure (mmHg) | Short | 76.63 ± 5.88 | 74.00 ± 7.19 | 73.88 ± 8.13 | 76.75 ± 8.70 | 0.288 (0.16) | 0.331 (0.14) | 0.584 (0.09) |
| | Medium | 72.38 ± 10.27 | 73.43 ± 12.39 | 73.75 ± 7.78 | 77.50 ± 9.44 | | | |
| | Long | 76.71 ± 6.37 | 76.25 ± 8.26 | 79.25 ± 8.22 | 79.00 ± 7.96 | | | |
| | Control | 72.71 ± 9.30 | 75.43 ± 9.50 | 75.86 ± 10.24 | 76.43 ± 7.41 | | | |
| Mood state | Short | 4.63 ± 0.74 | 3.63 ± 1.69 | 3.75 ± 1.67 | 4.25 ± 1.16 | 0.536 (0.06) | 0.710 (0.03) | 0.672 (0.05) |
| | Medium | 3.63 ± 1.51 | 3.75 ± 1.75 | 3.88 ± 1.46 | 3.75 ± 1.75 | | | |
| | Long | 4.25 ± 1.16 | 3.63 ± 1.85 | 3.50 ± 1.31 | 3.88 ± 1.73 | | | |
| | Control | 3.25 ± 1.28 | 3.88 ± 1.81 | 3.75 ± 1.49 | 3.63 ± 1.41 | | | |
| Motivation to exercise | Short | 13.38 ± 3.29 | 12.88 ± 3.56 | 12.50 ± 2.98 | 13.25 ± 2.82 | 0.473 (0.11) | 0.746 (0.05) | 0.375 (0.13) |
| | Medium | 12.63 ± 3.38 | 13.38 ± 3.50 | 13.25 ± 3.28 | 12.88 ± 3.18 | | | |
| | Long | 11.88 ± 5.59 | 10.38 ± 4.66 | 10.25 ± 5.20 | 11.75 ± 4.89 | | | |
| | Control | 12.38 ± 4.14 | 13.38 ± 2.97 | 13.38 ± 2.83 | 13.13 ± 1.96 | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Negative affect | Short | 10.13 ± 0.35 | 10.75 ± 1.39 | 10.75 ± 1.16 | 10.50 ± 0.76 | 0.411 (0.12) | 0.277 (0.16) | 0.444 (0.11) |
| | Medium | 10.25 ± 0.71 | 11.13 ± 2.10 | 11.13 ± 1.89 | 10.75 ± 1.39 | | | |
| | Long | 10.88 ± 1.13 | 11.00 ± 1.31 | 10.75 ± 1.16 | 10.50 ± 0.76 | | | |
| | Control | 10.50 ± 0.76 | 11.38 ± 1.77 | 11.00 ± 1.41 | 10.63 ± 1.19 | | | |
| Positive and negative affect ratio | Short | 2.98 ± 0.93 | 2.64 ± 1.19 | 2.59 ± 1.36 | 2.59 ± 1.31 | 0.346 (0.14) | 0.134 (0.28) | 0.793 (0.04) |
| | Medium | 2.69 ± 1.15 | 2.36 ± 1.41 | 2.46 ± 1.42 | 2.44 ± 1.36 | | | |
| | Long | 2.74 ± 1.24 | 2.65 ± 1.34 | 2.38 ± 1.19 | 2.36 ± 1.32 | | | |
| | Control | 2.78 ± 0.96 | 2.43 ± 1.11 | 2.39 ± 1.14 | 2.43 ± 1.32 | | | |

*Values are presented as group means ± SD.* Short = 15 × 2/2 mins; Medium = 10 × 3/3 mins; Long = 5 × 6/6 mins (hypoxia/normoxia).

SD, standard deviation; ANOVA, analysis of variance.

## 4.6. Discussion

This is the first study to compare the acute psycho-physiological responses to SHORT (15 × 2/2 mins), MEDIUM (10 × 3/3 mins) and LONG (5 × 6/6 mins) cyclical variations of IHE. During one 60-min (30 min hypoxia/30 min normoxia) IHE session, arterial and brain oxygenation decreases *versus* control, independently of cycle length. Compared to baseline, perceived breathlessness increased 15 min after IHE completion. This increase tended to be smaller following SHORT than LONG. When implementing IHE, greater desaturation is observed during longer compared to shorter hypoxic/normoxic cycles in adults with obesity. However, IHE tends to be better tolerated perceptually with shorter rather than longer cycles.

### *4.6.1. During IHE*

IHE decreased $SpO_2$ (during hypoxic cycles) *versus* control. Further, LONG (-7%) led to larger decreases than MEDIUM (-3%) and SHORT (-1%) *versus* normoxic cycles of each respective condition. Although the hypoxic duration was matched across IHE (30 mins), the extent of $SpO_2$ decrease is aligned with hypoxic/normoxic cycle length. This may be due to acute hypoxic exposure inducing a progressive decline in $SpO_2$ (Botek et al., 2018) that is more evident in longer *versus* shorter cycles. $SpO_2$ has been found to decrease continuously during exposure to hypoxia at rest ($FiO_2$ = 9.6%) for up to 10 mins *versus* a normoxic baseline in healthy individuals (-26% 0–10-min) (Krejčí et al., 2016). However, $SpO_2$ values during hypoxic cycles of IHE presented in the current study (SHORT = 94.2%; MEDIUM = 93.1%; LONG = 90.1%) may be considered clinically insignificant. Hence, $SpO_2$ below 90% has been defined as a state of hypoxemia (Basnet et al., 2006). To reach greater levels of desaturation (hypoxemic state) alone, it is likely that IHE protocols consisting of longer rather than shorter hypoxic/normoxic cycles would be recommended. Overall, cyclical variations of IHE impacts on the subsequent decreases in $SpO_2$, with longer cycles inducing lower values.

TSI of the pre-frontal cortex decreased during all IHE cycles in reference to control. Here, it was speculated that longer cycles of IHE would lead to larger decreases in pre-frontal cortex oxygenation *versus* shorter cycles (Verges et al., 2012), but this was not the case. Rupp et al. (2016) reported decreases in pre-frontal cortex oxygenation (-3%) and $SpO_2$ (-9%) during 2-min IHE cycles ($FiO_2$ = 11.0%) for 45 mins *versus* a normoxic baseline in healthy individuals, similar to the current study (TSI: -3%; $SpO_2$: -5%). Chacaroun et al. (2017) also reported decreases in cerebral oxygenation (-6%) during IHE (7 × 5-min hypoxia/3-min normoxia) at a target $SpO_2$ of 70–80%. Overall, it seems that larger $SpO_2$ decreases lead to measurable differences in pre-frontal cortex deoxygenation. A greater hypoxic dose than that used in the current study ($FiO_2$ = 12.0%) may have led to larger $SpO_2$ decreases, and as such, pre-frontal cortex oxygenation, during both SHORT and LONG. Notably, TSI decreases occurred and were maintained from T1–T5 *versus* T0. It was previously stated that more than 30 mins continuous hypoxic exposure is required to obtain quantifiable decreases in TSI of the pre-frontal cortex (Chacaroun et al., 2017). Under the present circumstances, IHE comprised of varying hypoxic cycles totaling 30-min induced similar deoxygenation levels in the pre-frontal cortex of adults with obesity, independent of cycle length, which was maintained for 60 mins. During IHE, no changes in perceived mood state, breathlessness and motivation to exercise between IHE cycles were reported or *versus* control. During a 21-day bed rest in hypoxia ($FiO_2$ = 15.0%), healthy individuals felt more depressed, tense and confused at days 14 and 21 *versus* baseline (normoxia) (Stavrou et al., 2018). Although IHE and bed rest are passive modalities, the negative affects during bed rest in combination with hypoxia are unlikely to occur during IHE due to reduced exposure duration and inclusion of normoxic cycles. It was previously reported that mood is negatively impacted during rest in continuous hypoxia (8 h; $FiO_2$ = 13.0%) *versus* baseline (normoxia) (de Aquino Lemos et al., 2016). Therefore, it was anticipated that SHORT would likely lead to better overall perception. However, no perceptual differences were observed between conditions during IHE. This may be due to differences in exposure type (intermittent *versus* continuous), duration (30 mins *versus* 8 h), the hypoxic dose between studies ($FiO_2$ = 12.0% *versus* 13.0%), or little hypoxemia. It can be concluded here that perceptual responses during IHE are maintained with all tested cycle variations.

### *4.6.2. Pre- and post-IHE*

Albeit with severe continuous hypoxic exposure ($FiO_2$ < 8.0%), elevations in blood pressure in humans and animals occur (White et al., 1985). Herein, the present study assessed blood pressure and found no differences between baseline and post-intervention following IHE of a moderate hypoxic level ($FiO_2$ = 12.0%). Previous studies have found normalized blood pressure in hypertensive patients following regular IHE (~1–5-min hypoxic/normoxic cycles, $FiO_2$ = 10.0–14.0%, daily for ~60 mins, 10–14 days) (Serebrovska et al., 2008). As there were no blood pressure assessments during IHE in the current study, the current dataset cannot support this evidence. No negative sympathetic nervous system activity effects are realized regardless of IHE cycle length and is thus considered a safe therapy.

One unique finding includes greater perception of breathlessness 15 mins post-exposure *versus* baseline, which tended to be exacerbated following LONG *versus* SHORT. It could be argued that this response occurred due to dyspnoeagenia, i.e., an evoked respiratory exertion without increased physiological ventilation (Ward & Whipp, 1989). In adults with obesity, breathlessness is a symptom often felt during rest (Gibson, 2000), which may explain the increases in perceived breathlessness following control and IHE. Importantly, increases in perceived breathlessness tended to be smaller following SHORT, and greater following LONG. In summary, shorter IHE cycles may be preferential over longer because of a marginal lowering in the magnitude of post-intervention increases in perceived breathlessness after IHE.

Compared to baseline, positive affect was reduced 15–60 mins post-intervention in all conditions (including control). Stavrou et al. (2018) found reduced positive affect following a

21-day bed rest in hypoxic and normoxic conditions. Perceived mood state, motivation to exercise and negative affect were maintained throughout IHE in the current study. As such, a reduced positive affect may not be due to hypoxia *per se* but the lack of activity over time (>3 h). Although positive affect was reduced following the 60-min intervention, it is unlikely that this was due to the effect of IHE, or in particular, cyclical variation.

### *4.6.3. Limitations and perspectives*

The current study has several limitations. Firstly, the sample size was small (n = 8) implying that the findings should be interpreted with caution. Conclusions from this data are made only from stage I obesity, which may differ to stage II and III, and between genders such as larger psychophysiological stress (Stengel et al., 2013). Secondly, one hypoxic dose ($FiO_2$ = 12.0%) was used throughout IHE. Further studies should verify whether a more severe $FiO_2$ (lower than that used in the current study) during longer hypoxic/normoxic cycles, which will likely maximise the desaturation achieved during IHE, does not lead to negative effects on perceptual responses. IHE combined with exercise may potentiate further positive responses, at least short-term, than IHE alone due to added physical activity. As such, chronic studies implementing 2-min IHE (and exercise) cycles on a regular basis (3–4 times per week, over 4–6 weeks) (Hobbins et al., 2017) which are likely to improve aspects of health, are needed since the current study is acute-focused. The findings of this study shed some light on disregarded perceptual responses.

## **4.7. Conclusion**

When implementing IHE, greater desaturation is observed during longer compared to shorter hypoxic/normoxic cycles in adults with obesity. However, IHE tends to be better tolerated perceptually with shorter rather than longer cycles.

### 4.8. Importance of findings for subsequent chapter and thesis

The findings of the current study have highlighted that IHE can be optimised for acute, positive physiological and psychological responses in obese individuals. However, combining exercise with IHE maybe a more potent physiological and psychological stimulus to induce larger beneficial responses in this at-risk population. Using the optimal IHE cycle duration found in the current study (15 × 2/2 mins), it could be that exercising in a hypoxic environment intermittently is better than a normoxic environment for the same intermittent and total exercise duration on psycho-physiological responses in obese individuals.

Given the current health risks to obese individuals prior, during and following the completion of exercise, it can be considered necessary to identify the psycho-physiological responses to interval exercise in hypoxia *versus* normoxia in healthy individuals. Naturally, the health risks to these individuals is relatively lower, but findings of this investigation will provide a proof of concept for the future inclusion of obese individuals.

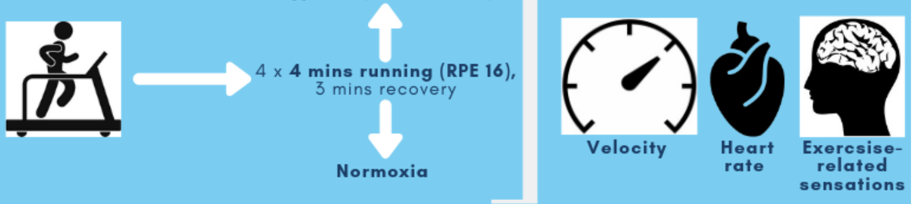
# 5. Psycho-physiological responses to perceptually-regulated interval runs in hypoxia and normoxia

## 5.1. Graphical abstract

### Aim

To investigate the effect of HIIT at a clamped RPE of 16 (typically used by athletes during HIIT) in hypoxia and normoxia on adjustments in running velocity and associated exercise-related sensations of trained runners.

### Methods



**Hypoxia** (FiO2 = 15.0%)

4 x **4 mins running (RPE 16)**, 3 mins recovery

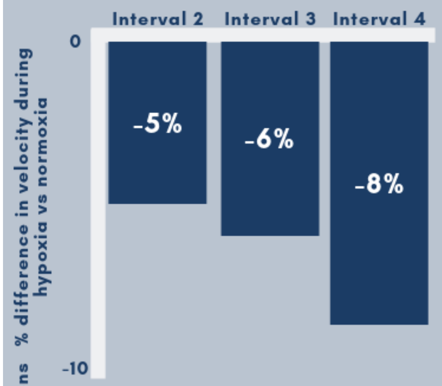
**Normoxia**

**Velocity**

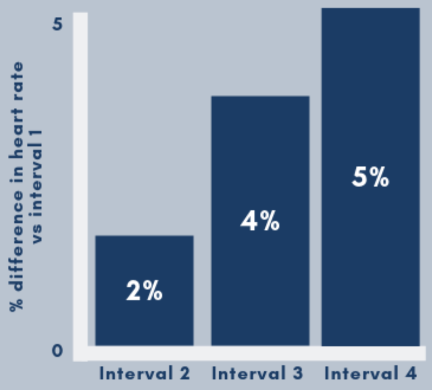
**Heart rate**

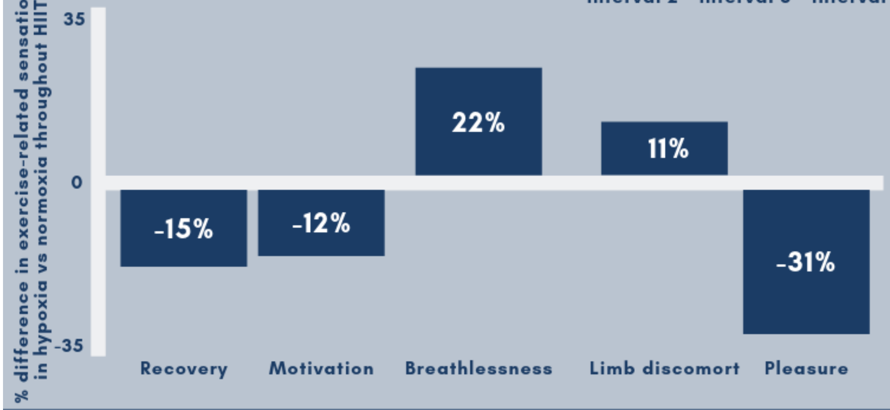
**Exercsise-related sensations**

### Results



*not different between hypoxia and normoxia





### Conclusions

When carrying out HIIT at a perceptually-regulated intensity (RPE = 16), progressively larger running velocity decreases are needed in hypoxia than normoxia. This is accompanied by similar physiological stress (i.e., HR) yet higher-than-normal exercise-related sensations in hypoxia vs. normoxia.

**Created by Liam Hobbins on canva.com**

## 5.2. Abstract

**Aim** Whether perceptually-regulated high-intensity intervals in hypoxia are associated with slower running velocities *versus* normoxia, when physiological responses and exercise-related sensations remain the same.

**Methods** Nineteen trained runners (33.4 ± 9.1 years) completed a high-intensity interval running protocol (4 × 4-min intervals at a clamped perceived rating exertion of 16 on the 6–20 Borg scale, 3-min passive recoveries) in either hypoxic (HYP; $FiO_2 = 15.0\%$) or normoxic (NOR; $FiO_2 = 20.9\%$) conditions.

**Results** Participants adjusted to a progressively slower running velocity from interval 1–4 (-7.0%), and more so in HYP *versus* NOR for intervals 2, 3 and 4 (-4.6%, -6.4% and -7.9%, respectively; $p < 0.01$). Heart rate increased from interval 1–4 (+4.8%; $p < 0.01$), independent of condition. $SpO_2$ was lower in HYP *versus* NOR (86.0% *versus* 94.8%; $p < 0.01$). Oxyhemoglobin (-23.7%) and total hemoglobin (-77.0%) decreased, whilst deoxyhemoglobin increased (+44.9%) from interval 1–4 ($p < 0.01$), independent of condition. Perceived recovery (-41.6%) and motivation (-21.8%) were progressively lower from interval 1–4, and more so in HYP *versus* NOR for intervals 2, 3 and 4 (recovery: -8.8%, -24.2% and -29.3%; motivation: -5.3%, -20.3% and -22.4%, respectively; $p < 0.01$). Perceived breathlessness (+18.6%), limb discomfort (+44.0%) and pleasure (-32.2%) changed from interval 1–4, with significant differences (+21.8%, +11.3% and -31.3%, respectively) between HYP and NOR ($p < 0.01$).

**Conclusions** Slower interval running velocities in hypoxia achieve similar heart rate and muscle oxygenation responses to those observed in normoxia when perceptually-regulated, yet at the expense of less favourable exercise-related sensations.

## 5.3. Introduction

HIIT in normobaric hypoxia is receiving attention for its potential in further advancing athletic performance compared to HIIT in normoxia. Buchheit et al. (2012) employed a HIIT protocol (3 × 5-min, 90-s recovery) carried out in hypoxia ($vVO_{2Max}$ = 84%; $FiO_2$ = 15.4%) and normoxia ($vVO_{2MAX}$ = 90%) at a fixed-intensity (determined in normoxia) in highly-trained runners. A reduced physiological stress (i.e., lower HR) was observed during hypoxia compared to normoxia, likely due to a lower $vVO_{2Max}$ in hypoxia *versus* normoxia. However, fixed exercise intensities, regardless of environmental conditions, intuitively do not permit adjustments (i.e., increases or decreases of workload) during exercise to match the intensity target (i.e., $vVO_{2MAX}$). In turn, over-induced physiological stress may be counter-productive (i.e., greater [HHb], lower [$O_2$Hb]) for intended session goals (Laurent et al., 2014). Furthermore, matched absolute fixed exercise intensities (i.e., a similar percentage of $vVO_{2MAX}$) lead to greater physiological stress (i.e., compensatory increase in HR) in hypoxia compared to normoxia due to reduced $FiO_2$ (Heinonen et al., 2016). Perceptually-regulated exercise intensities, that allow velocity adjustments based upon exercise-related sensations in order to maintain a target effort level, may offer a viable solution, and is perhaps more reflective of how exercisers modify intensity during acute exercise.

Perceptually-regulated exercise permits the individual exercising to self-regulate external workload (i.e., running velocity/cycling power production) based upon Borg's RPE scale (Parfitt et al., 2012). The validity and usefulness of using RPE for perceptually-regulating exercise has been described (Hardy & Rejeski, 1989). The reduced oxygen availability in hypoxia makes the expectation tenable that there would be a slower self-selected running velocity in hypoxia for a given RPE, while velocity in normoxia would be more preserved, as evidenced previously (Fernández Menéndez et al., 2018). Chacaroun et al. (2018) demonstrated for a lower power output (-15%), *vastus lateralis* muscle [HHb] was higher and

[$O_2Hb$] lower in hypoxia ($FiO_2$ = 13.5%) compared to normoxia during a single interval session (15 × 1-min at 75% of $HR_{MAX}$, 1-min recoveries). Although HR was similar between conditions, RPE has been reported to be higher in hypoxia compared to normoxia during fixed-intensity interval runs (Buchheit et al., 2012) and repeated-sprint cycling (Brocherie et al., 2017). Employing self-paced exercise, in replace of fixed-intensity exercise, may assist in overcoming the over-excessive physiological stress observed when exercising in hypoxia *versus* normoxia, due to the likelihood of greater velocity preservations in the latter than the former.

In normoxia at pre-determined fixed intensities, HIIT is perceived as more enjoyable compared to moderate-intensity continuous running (Thum et al., 2017). However, during HIIT at fixed-intensities, exercise-related sensations decrease when the exercise intensity rises above threshold preference (Lind et al., 2005). Further, HIIT in hypoxia at fixed-intensities typically surpasses the preferred threshold in normoxia (Friedmann et al., 2004). Implementing a self-paced exercise model may permit modifications required (i.e., slower running velocities) to maintain exercise-related sensations contributing to RPE (Abbiss et al., 2015) in hypoxia and normoxia. Cycling continuously for 10 mins at a fixed-intensity (corresponding to 50% $VO_{2MAX}$) in hypoxia *versus* normoxia negatively impacts cognitive function (Ochi et al., 2018). Slower self-selected running velocities may assist with mitigating hypoxic-induced negative cognitive function compared to normoxia (McMorris et al., 2017). These potential findings may benefit athletes exercising intensely in hypoxia, shortly followed by skills requiring attention and accuracy.

Therefore, the aim of this study was to investigate the effect of HIIT at a clamped RPE of 16 (typically used by athletes during HIIT) (Seiler & Sjursen, 2004) in hypoxia and normoxia on adjustments in running velocity and associated exercise-related sensations of trained runners. It was hypothesised that running velocity would be progressively slower in hypoxia compared to normoxia across intervals, whilst physiological and cognitive responses and exercise-related sensations would not differ between conditions. Decreasing external load with matched internal load during perceptually-regulated HIIT in hypoxia compared to normoxia may benefit athletes during heavy training blocks prior to competition.

## 5.4. Methods

### *5.4.1. Participants*

Nineteen trained runners (3 females, 16 males; age: 33.4 ± 9.1 years; height: 176 ± 8 cm; weight: 76.3 ± 10.9 kg; BMI: 24.5 ± 2.1 kg/m) provided written informed consent to participate. This study received ethical approval from the Ethics Committee of the Anti-Doping Lab Qatar institutional review board (Agreement SCH-ADL-170).

### *5.4.2. Experimental design*

Participants reported to the laboratory on three occasions, each separated by ≥48 h. The first session included study familiarisation. The second and third visits included completing a perceptually-regulated HIIT protocol (4 × 4-min intervals at a clamped perceived rating exertion of 16 on the 6–20 Borg scale, 3-min passive recoveries) in either hypoxia ($FiO_2$ = 15.0%) or normoxia in a randomised, counterbalanced order. Physiological responses (HR, $SpO_2$, muscle oxygenation) were continuously assessed during intervals, perceptual responses (recovery, motivation, breathlessness, limb discomfort and pleasure) before and after, and physiological (blood lactate) and cognitive responses before and after the HIIT protocol. Participants were instructed to refrain from any intense exercise 48 h prior to each visit and consume their last meal at least 2 h prior to the HIIT sessions.

### *5.4.3. Familiarisation session*

At the preliminary visit to the laboratory, participants were familiarised with the perceptual scales and cognitive test. The running velocity individually associated as an RPE of 16 was determined for each participant in normoxia (3.6.). After 10 mins of rest, participants completed one 4-min interval composing the HIIT protocol (see below) for habituation.

### *5.4.4. Experimental trials*

Participants completed two experimental trials in normoxia (NOR; $FiO_2$ = 20.9%) and hypoxia (HYP; $FiO_2$ = 15.0%, equivalent to ~2700 m above sea level). After a standardised warm up (5 mins at 10 km/h), a facemask connected to a portable hypoxic generator (3.8.) was attached. Participants rested for 1-min (quiet standing) before a 1-min run at their velocity associated with an RPE = 16. Participants then rested for 3 mins before completing the HIIT protocol. The HIIT protocol was based upon aerobic interval-training (Gibala et al., 2014) and carried out on a motorised treadmill (ADAL3D-WR, Medical Development–HEF Tecmachine, France). Participants completed four, 4-min intervals, interspersed with 3-min recoveries (quiet standing). The first 30 s of each 4-min interval began at participants' individual velocity. Participants were then free to decide if or how treadmill velocity needed to be adjusted (manually by one experimenter) to ensure maintenance of an RPE of 16 every 30 s (3.7).

### *5.4.5. Hypoxic conditioning*

Participants were fitted with a facemask fastened with a Velcro headset connected *via* plastic tubing to a hypoxic generator (AltiTrainer, SMTec SA, Nyon, Switzerland) to create hypoxia. The gas mixing system enriches inspired air by adding a fixed quantity of nitrogen *via* a 30-L mixing chamber, with the dilution being constantly controlled by a $PO_2$ probe (precision = T0.82 torr, safety $FiO_2$ = 9.7%). Total hypoxic exposure corresponded to exactly 28 mins during HYP.

### *5.4.6. Measures*

#### *5.4.6.1. During HIIT*

Treadmill velocity, HR (3.9.1.) and $SpO_2$ (3.9.2.) were manually recorded every 30 s during each 4-min interval.

Muscle oxygenation trends of the *vastus lateralis* muscle were recorded using NIRS (Portalite, Artinis, Netherlands) in real-time (3.9.4.). Bi-polar optode sensors were attached approximately 10 cm above the proximal border of the patella *via* double-sided adhesive tape and housed (3 cm apart, 775 Nm wavelength) within rubber-cased hoods.

Perceived recovery (3.11.1.) and motivation to exercise (3.11.2.) were assessed 30 s before each 4-min interval. Recovery was assessed before the first interval to determine perceptions following the warm up. Immediately after each 4-min interval, ratings of perceived breathlessness (3.11.3.), limb discomfort (3.11.4.) and pleasure (3.11.5.) were assessed.

#### *5.4.6.2. Pre- and post-HIIT*

A capillary blood sample taken from the fingertip was analysed for $[La^+]$ (3.10.2) immediately before the warm-up and 2 min after HIIT. Cognitive function was assessed after $[La^+]$ *via* the Stroop colour-word test (3.12.1.).

### *5.4.7. Data analysis*

Data were processed offline into Excel (Microsoft Office, 2016). Velocity, HR and $SpO_2$ values were averaged across each 4-min interval. Muscle oxygenation parameters were smoothed using a 5-point moving average. The last 30 s of each 4-min interval were averaged and normalized to the 30-s rest period before the first interval (reference values) for each respective condition and then presented as absolute change in $[O_2Hb]$, [HHb] and [tHb] (Chacaroun et al., 2018). Cognitive function data were averaged across the test duration.

### *5.4.8. Statistical analysis*

A two-way ANOVA was used to investigate the main effect of condition (HYP *versus* NOR), time (pre *versus* post or interval 1 *versus* 2, 3, and 4) and the condition × time interaction.

## 5.5. Results

### *5.5.1. During HIIT*

#### *5.5.1.1. Velocity*

Compared to interval 1, participants adjusted to a progressively slower running velocity during intervals 2, 3 and 4 (-2.8%, -5.2% and -7.0%, respectively; $p < 0.01$), and more so in HYP *versus* NOR for intervals 2, 3 and 4 (-4.6%, -6.4% and -7.9%, respectively; $p < 0.01$; Figure 5.1.A).

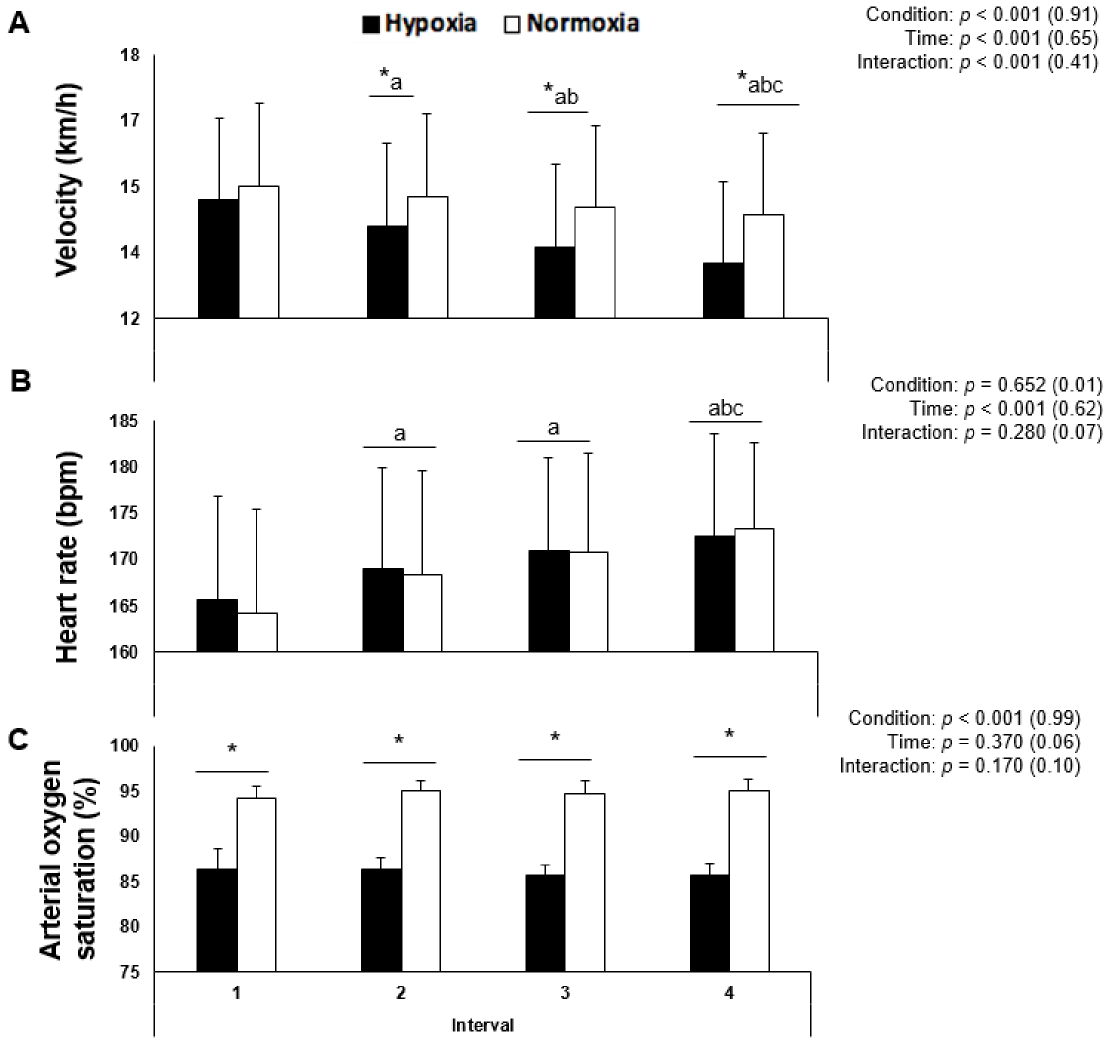


**Figure 5.1.** Changes in velocity (A), heart rate (B) and arterial oxygen saturation (C) during the high-intensity intermittent running protocol. Data are presented as mean ± SD. ANOVA main effects of time, condition and interaction are presented along with partial-eta squared for effect size into brackets. Black bars = hypoxic condition; white bars = normoxic condition. * denotes a statistically significant difference between conditions for a given interval ($p < 0.05$), a, b and c denotes a statistically significant difference *versus* interval 1, 2 and 3, respectively ($p < 0.05$).

#### *5.5.1.2. HR and $SpO_2$*

Compared to interval 1, HR increased during intervals 2, 3 and 4 (+2.3%, +3.6% and 4.8%, respectively; $p < 0.01$; Figure 5.1.B), independently of condition ($p = 0.65$). $SpO_2$ was globally lower in HYP *versus* NOR (-9.3% average across intervals; $p < 0.01$; Figure 5.1.C), independently of time ($p = 0.37$).

#### *5.5.1.3. Muscle oxygenation*

From interval 1 to 4, [$O_2$Hb] and [tHb] decreased (-23.7% and -77.0%, respectively) whilst [HHb] increased (+44.9%; $p < 0.01$; Figures 5.2.A–C), independently of condition ($p > 0.08$).

#### *5.5.1.4. Perceptual responses*

Perceived recovery decreased progressively from interval 1 to 4 (-41.6%; $p < 0.01$), and more so in HYP *versus* NOR before intervals 2, 3 and 4 (-8.8%, -24.2% and -29.3%, respectively; $p = 0.02$; Figure 5.3.A). Perceived motivation decreased progressively from interval 1 to 4 (-21.8%; $p < 0.01$), and more so in HYP *versus* NOR before intervals 3 and 4 (-20.3% and -22.4%, respectively; $p < 0.01$; Figure 5.3.B). Compared to interval 1, perceived breathlessness increased following intervals 2, 3 and 4 (+14.0%, +13.6% and +18.6%, respectively; $p < 0.01$; Figure 5.3.C), independently of condition. Breathlessness was rated globally higher in HYP *versus* NOR (+21.8%; $p < 0.05$), irrespective of time. Compared to interval 1, perceived limb discomfort increased following intervals 2, 3 and 4 (+23.3%, +35.3% and +44.0%, respectively; $p < 0.01$; Figure 5.3.D), independently of condition. Limb discomfort was rated globally higher in HYP *versus* NOR (+11.3%; $p = 0.01$), irrespective of time. The time-dependent decreases in perceived pleasure across intervals (-14.7%, -25.4% and -32.3%, intervals 2, 3 and 4 *versus* 1, respectively; $p < 0.01$; Figure 5.3.E) tended to be larger in HYP *versus* NOR (-31.3%, $p = 0.06$).

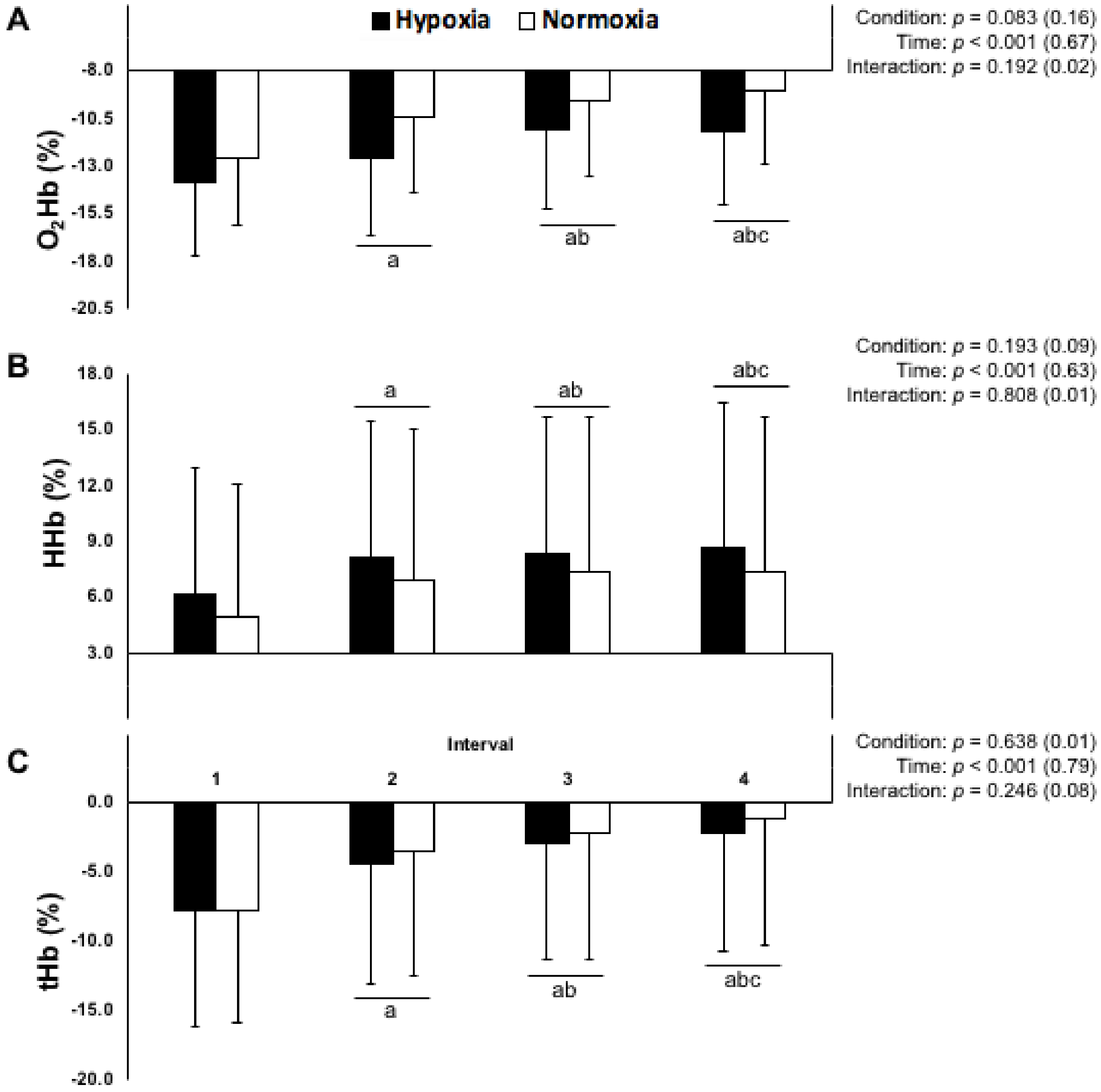


**Figure 5.2.** Changes in Oxygenated (A; $O_2Hb$), deoxygenated (B; HHb) and total hemoglobin (C; tHb) during the high-intensity intermittent running protocol. Data are calculated as a percentage difference from baseline (%) and presented as mean ± SD. ANOVA main effects of time, condition and interaction are presented along with partial-eta squared for effect size into brackets. Black bars = hypoxic condition; white bars = normoxic condition. a, b and c denotes a statistically significant difference *versus* interval 1, 2 and 3, respectively ($p < 0.05$).

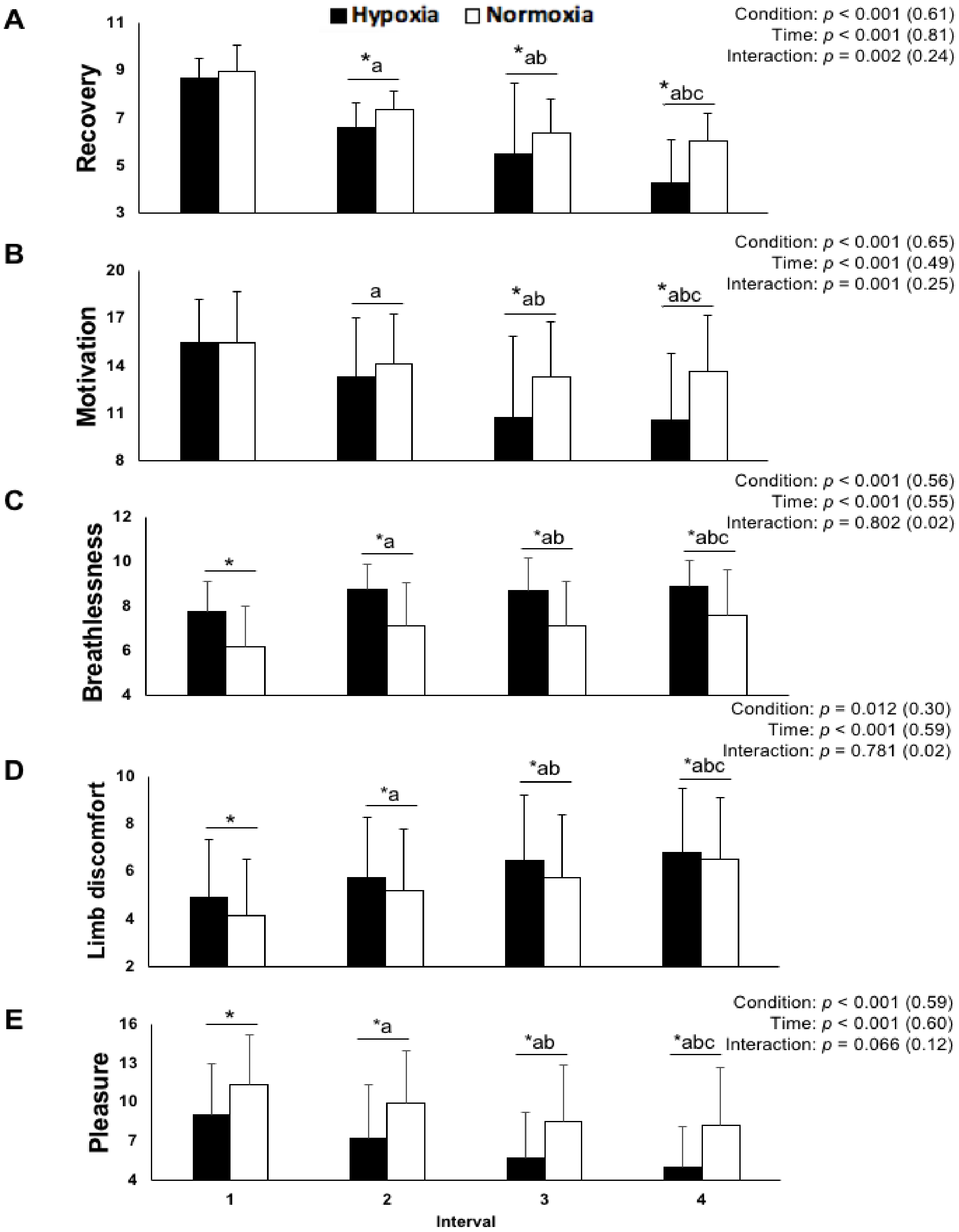


**Figure 5.3.** Changes in perceived recovery (A), motivation (B), breathlessness (C), limb discomfort (D) and pleasure (E) during the high-intensity intermittent running protocol. Data are presented as mean ± SD. ANOVA main effects of time, condition and interaction are presented along with partial-eta squared for effect size into brackets. Black bars = hypoxic condition; white bars = normoxic condition. * denotes a statistically significant difference between conditions for a given interval ($p < 0.05$), a, b and c denotes a statistically significant difference *versus* interval 1, 2 and 3, respectively ($p < 0.05$).

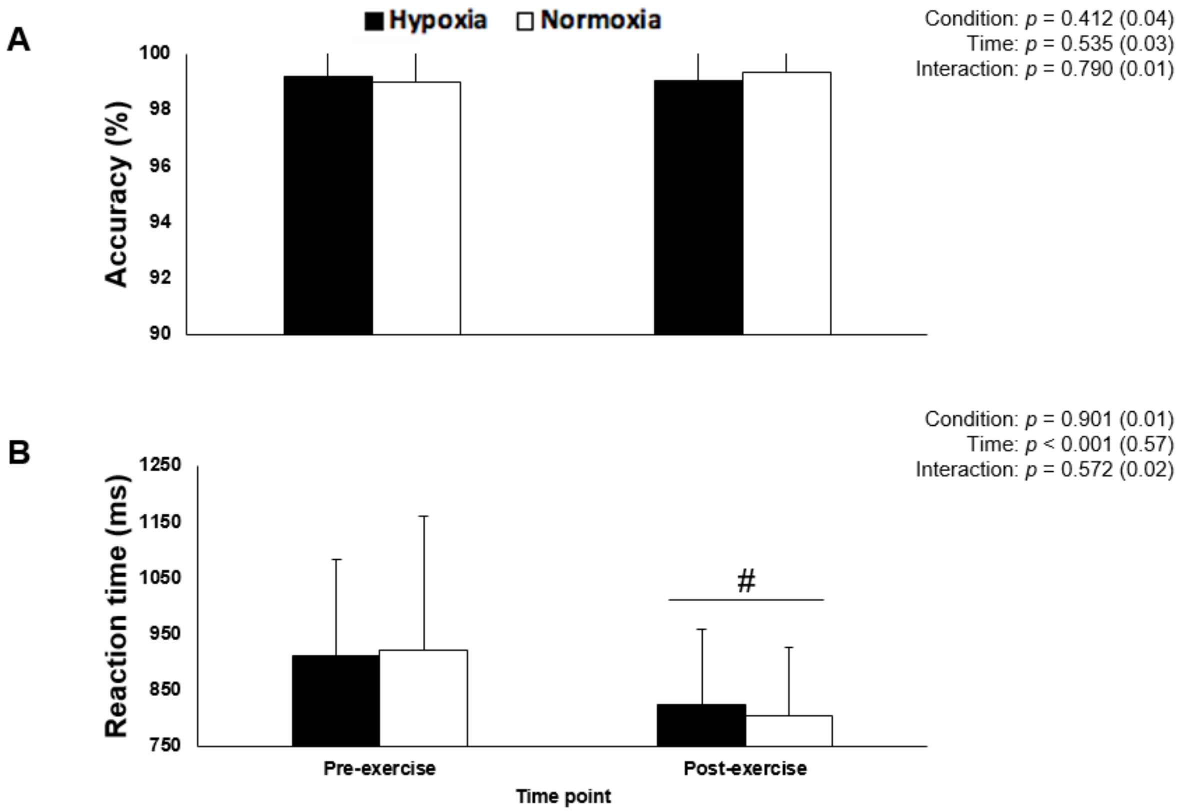


**Figure 5.4.** Changes in accuracy (A) and reaction time (B) pre and post high-intensity intermittent running protocol. Data are averaged over 3 mins and presented as mean ± SD. ANOVA main effects of time, condition and interaction are presented along with partial-eta squared for effect size into brackets. Black bars = hypoxic condition; white bars = normoxic condition. # denotes a statistically significant difference *versus* pre-exercise ($p < 0.01$).

### *5.5.2. Pre- and post-HIIT*

### *5.5.2.1. Blood lactate*

The pre- to post-exercise increase in [$La^+$] was larger ($p = 0.001$) in HYP (1.7 ± 0.8 *versus* 13.1 ± 3.8 mmol/l) *versus* NOR (2.1 ± 0.9 *versus* 10.1 ± 3.9 mmol/l).

### *5.5.2.2. Cognitive function*

During the Stroop test, accuracy was unaffected by condition and time (Figure 5.4.A). Participants' reaction time was faster (+11%) post *versus* pre HIIT ($p < 0.01$; Figure 5.4.B), independently of condition.

## 5.6. Discussion

Using a perceptually-regulated (RPE = 16) exercise model, it was observed that: 1) participants ran progressively slower during HIIT with larger decreases in HYP *versus* NOR, 2) HR and muscle oxygenation trends (during intervals) and cognitive responses (pre *versus* post HIIT) were similar between conditions, 3) greater breathlessness and limb discomfort, and lower recovery, motivation and pleasure scores were stated during recovery between HYP *versus* NOR, and 4) blood lactate concentration was larger after HYP *versus* NOR. Overall, using a manipulation of oxygen availability, a reduced external workload (i.e., running velocity) during perceptually-regulated interval running is associated with a similar internal load (i.e., physiological responses). Although no cognitive function differences were found between conditions, this is achieved with less favourable exercise-related sensations. A matched internal workload for a decreased external workload during perceptually-regulated HIIT in hypoxia *versus* normoxia may assist athletes to reach intended session goals with minimal over-induced physiological stress. However, perceptually-regulated HIIT exacerbates exercise-related sensations and metabolic stress (i.e., [$La^+$]) in hypoxia compared to normoxia. This may then have negative carry-over effects on training responsiveness in the following days.

### *5.6.1. During HIIT*

The velocity deemed equal to RPE 16 was as expected for trained runners (~15 km/h) (da Silva et al., 2015). Interestingly, running velocity did not differ between conditions during the first HIIT interval, despite lower $SpO_2$ in hypoxia *versus* normoxia. Smith & Billaut (2010) found maintained $SpO_2$ during repeated-sprinting in normoxia (20 × 5 s all out, 25 s recovery) until after the fifth sprint in national-level soccer players, whereby peak power significantly decreased compared to sprint one. Overall, it seems that initial decreases in $SpO_2$ (within interval one) do not necessarily impact on HIIT compared to sprint intervals.

It was found that participants selected a progressively slower running velocity during HIIT in both conditions. In highly-trained middle to long-distance runners, a 6% reduction in $vVO_{2MAX}$ when running in hypoxia *versus* normoxia is acceptable to match the acute physiological stress induced (Buchheit et al., 2012). It can be suggested that self-selected velocity adjustments found in the current study to maintain RPE 16 are matched with modifications in hypoxic *versus* normoxic training sessions employed by coaches and sport scientists for athletes (Dufour et al., 2006). Decreased external workloads have been reported by Pramsohler et al. (2017) during continuous cycling (seven 30-min sessions over 3-wk), whereby participants cycled at -28% lower power output in hypoxia ($FiO_2$ = 15.3%) *versus* normoxia for a similar HR. Differences in these findings and ours may be due to the inclusion of geriatric patients completing pre-set (in normoxia) fixed-intensity cycling compared to trained runners self-regulating HIIT in the current study. However, Fernández-Menéndez et al. (2018) reported preferred walking velocity (RPE = 10) in hypoxia ($FiO_2$ = 15.3%) was 7% slower than normoxia in adults with obesity over 3 weeks. Using a self-paced model, irrespective of RPE target, population demographics and training block duration, lower external workloads are selected in hypoxia compared to normoxia. Overall, decreases in self-paced running velocity occurred to a greater extent in hypoxia than normoxia to maintain RPE 16, suggesting of a lower external workload. This finding may be of benefit to athletes who are unable or advised by their coach not to be training at a full intensity. Completing perceptually-regulated HIIT in hypoxia that requires slower running velocities compared to normoxia may in turn minimise mechanical constraints and eventually injury risk.

The present dataset shows that HR increased progressively during HIIT, irrespective of condition. This matches the hypothesis that HR will be comparable between hypoxia and normoxia, even though running velocity was lower in hypoxia. Other studies employing moderate continuous-intensity exercise have also found matched HR responses between hypoxic and normoxic training interventions (~4 weeks) when cycling at a -21.0% power output in healthy males (Haufe et al., 2008) and walking/running at a -17.5% velocity in obese adults (Wiesner et al., 2010) in hypoxia *versus* normoxia. Although exercise intensities in these studies were fixed, it could be suggested that increases in HR between conditions occur due to the environmental stressor (hypoxia) augmenting autonomic cardiac regulation (Krejčí et al., 2018). Overall, it seems self-paced exercise in hypoxia provides an added environmental stressor that is able to mimic HR responses in normoxia for a lower external load.

Lower [$O_2$Hb] and [tHb], and greater [HHb] of the *vastus lateralis* were recorded across HIIT, irrespective of condition. Decreases in [$O_2$Hb] and increases in [HHb] were expected during HIIT as oxygen delivery is outweighed by utilisation, whilst decreases in [tHb] reflect a lower localised blood flow (Van Beekvelt et al., 2001). Active musculature oxygenation is negatively impacted during fixed-intensity exercise in hypoxia compared to normoxia due to a lower $FiO_2$ (Heinonen et al., 2016). In support of this, Chacaroun et al. (2018) reported lower [$O_2$Hb] and greater [HHb] with maintained [tHb] of the *vastus lateralis* during fixed, relative high-intensity cycling in hypoxia (85% maximal power output in normoxia; $FiO_2$ = 13.5%) *versus* normoxia. Where a self-paced exercise model was employed here, similar [$O_2$Hb] and [HHb] responses are achieved between conditions. This is likely explained through the decreased external workload (i.e., slower running velocity) in hypoxia compared to normoxia, subsequently lowering oxygen utilisation. Discrepant findings in [tHb] may be due to different exercise modalities (cycling *versus* running) modifying blood flow regulation (Joyner & Casey, 2015). Similar to HR responses (central) previously discussed, it can be suggested here that local (tissue oxygenation) physiological stress is matched between conditions during HIIT in hypoxia at a slower velocity compared with normoxia.

Perceptual responses to HIIT were negatively impacted (i.e., lower recovery, and motivation) when assessed before intervals, with further exacerbations in hypoxia. Participants were instructed to maintain an RPE of 16 throughout HIIT by adjusting their velocity where necessary. It might be surprising at first that perceptual responses were worse in hypoxia compared to normoxia. However, perceived recovery and motivation are important affects associated with exercise intensity regulation (Renfree et al., 2014). The present results indicate that hypoxia negatively impacts these affects during HIIT compared with normoxia. This may be explained through lower perceived capabilities of hypoxic HIIT completion over normoxia (Stork et al., 2018), lowering perceived recovery and motivation. Further, although not assessment in the current study, it could be postulated that cerebral deoxygenation was greater during HIIT in hypoxia *versus* normoxia, as demonstrated by Subudhi et al. (2007) during incremental cycling. Accordingly, cerebral deoxygenation during HIIT may contribute to an integrative decision regarding negative perceptions, in which hypoxia hastens this effect (Subudhi et al., 2009). Given that the perceptually-regulated exercise model is governed centrally, this may provide a potential explanation as to why exercise-related sensations were more elevated in the hypoxic trial. Overall, it could be postulated that there is a disconnection between RPE and exercise-related sensations (i.e., recovery and motivation). Further research should look to optimise HIIT in hypoxia for positive perceptual responses.

Perceptual responses after intervals were negatively impacted (i.e., higher breathlessness and limb discomfort, lower pleasure), and to a further extent in hypoxia than normoxia. Buchheit et al. (2012) reported that 3-min absolute-intensity running intervals (84% $vVO_{2MAX}$) in hypoxia ($FiO_2$ = 15.4%) led to larger perceived limb discomfort compared to a lower absolute intensity in normoxia (90% $vVO_{2MAX}$). It was expected that exercise-related sensations would be similar between conditions as participants could adjust their velocity where necessary. However, this was not the case. Similar responses have been shown elsewhere (Christian et al., 2014), with greater perceived overall discomfort, breathlessness and limb discomfort following progressive, sub-maximal, self-paced cycling intervals (RPE = 3; modified CR10 Borg scale) in hypoxia ($FiO_2$ = 13.0%) compared to normoxia at a similar power output. Perceived breathlessness, limb discomfort and pleasure are exercise-related sensations contributing to overall RPE during exercise (Abbiss et al., 2015). However, there is a detachment between these when immediately assessed after HIIT intervals. Therefore, it could be suggested that self-paced HIIT in hypoxia leads to unfavourable exercise-related sensations before and after running intervals, compared to normoxia.

### *5.6.2. Pre- and post-HIIT*

Elevations in [$La^+$] following HIIT were higher in HYP than NOR. Values in the current study (10–13 mmol/l) are somewhat higher than those (5–6 mmol/l) reported elsewhere following a single HIIT session (6 × 4-min intervals at a RPE ~17, 4-min recoveries) (Seiler & Sjursen, 2004). This may be due to a 1/0.75 work/rest ratio implemented during the current protocol compared to 1/1 employed by Seiler & Sjogren (2004). [$La^+$] normalization during shorter recovery periods may not occur to the extent following longer recovery periods due to excess pyruvate accumulation (Howlett et al., 1999). This suggests that HIIT in hypoxia *per se* leads to increased [$La^+$] at slower running velocities compared to normoxia for similar physiological stress amounts. Practitioners should be aware that perceptually-regulated HIIT in hypoxia is a viable method for matching indices of physiological stress to normoxia. However, the blood lactate concentration increases after exercise were larger in hypoxia compared to normoxia. This may have negative implications on the muscle fatigue recovery process.

During the Stroop test, alertness increased (i.e., faster reaction time) whilst accuracy was maintained following HIIT, irrespective of condition. It is well known that HIIT in normoxia generally increases cognitive performance *versus* rest (i.e., faster reaction time, better accuracy) (Lambourne & Tomporowski, 2010). However, during fixed-intensity exercise in hypoxia, cognitive performance (i.e., attention and executive function) is worsened compared to normoxia (Ochi et al., 2018, McMorris et al., 2017). It can be reported that even though exercise-related sensations were worsened during HIIT, cognitive performance (assessed post-HIIT) was not negatively affected. Ochi et al. (2018) reported decreased Stroop performance 15 mins after 10 mins of moderate-continuous intensity exercise (50% peak oxygen uptake) in hypoxia ($FiO_2$ = 13.5%) *versus* normoxia. The current results likely differ to the aforementioned study due to cognitive testing performed in normoxia and following different exercise modalities. Overall, alertness is increased following HIIT, and not negatively impacted by hypoxia.

### *5.6.3. Limitations and perspectives*

During self-paced exercise at a perceptually-regulated intensity in hypoxia, HR and muscle oxygenation responses are similar to normoxia for a lower running velocity. However, a single "hypoxic dose" (i.e., hypoxic severity and duration), target RPE and exercise duration was utilised during HIIT. Further investigations should refine self-selected protocols in hypoxia, such as the "hypoxic dose", target RPE and exercise duration to minimise the negative side effects of worsened exercise-related sensations found under the present circumstances. In addition, whether there are gender differences in response to hypoxic exposure during perceptually-regulated HIIT should be investigated, given that the final sample size (n = 19) included only three females.

## 5.7. Conclusion

When carrying out HIIT at a perceptually-regulated intensity (RPE equal to 16), larger running velocity decreases are needed in hypoxia than normoxia. This is accompanied by similar physiological stress (i.e., HR and muscle oxygenation) during HIIT, and cognitive function adjustments after. In hypoxia, exercise-related sensations and blood lactate concentrations were higher-than-normal with larger arterial oxygen desaturation. Overall, perceptually-regulated running velocity in hypoxia compared to normoxia may be an effective alternative, at the expense of less favourable exercise-related sensations. The results suggest that athletes under the influence of hypoxia require lower external workloads to reach a perceptually-regulated target during HIIT than normoxia. If employed in a practical setting, coaches should consider the potential of negatively implicated exercise-related sensations and blood lactate concentrations which may have further negative carry-over effects on training responsiveness in the following days.

### 5.8. Importance of findings for subsequent chapter and thesis

The findings of this study have demonstrated the potential usefulness of decreasing the external workload during HIIT for a matched internal workload in hypoxia *versus* normoxia. As discussed, this may benefit athletes during particular periods throughout their training regime. Moreover, this finding may also be of benefit to obese individuals, given that exercise is generally perceived as difficult to complete.

Importantly, the negative affect that HIIT in hypoxia has on exercise-related sensations compared with normoxia should not go unnoticed. The first study of the current thesis concluded that shorter hypoxic/normoxic cycles leads to lower desaturation but better perceptual tolerance compared to longer cycles. It could be that this ratio (15 × 2/2 mins) would be more appropriate for interval/rest durations in obese individuals compared to a longer interval duration (4 × 4/3 mins) in the current study.

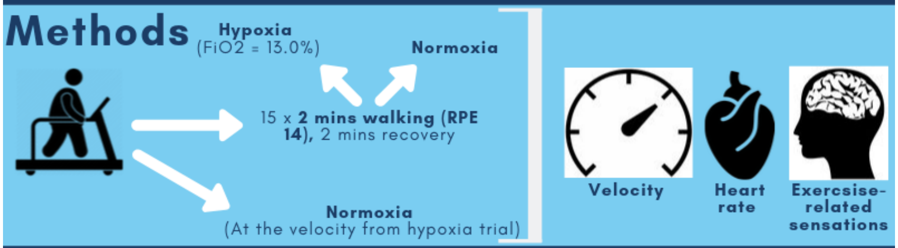
# 6. Psycho-physiological responses to perceptually-regulated hypoxic and normoxic interval walking in obese individuals

## 6.1. Graphical abstract

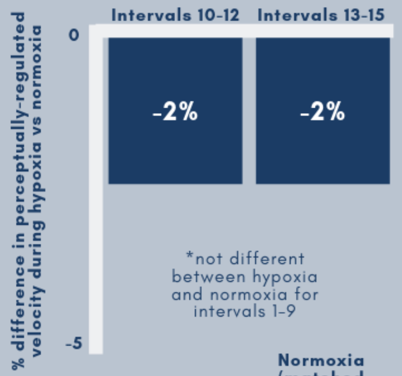
### Aim

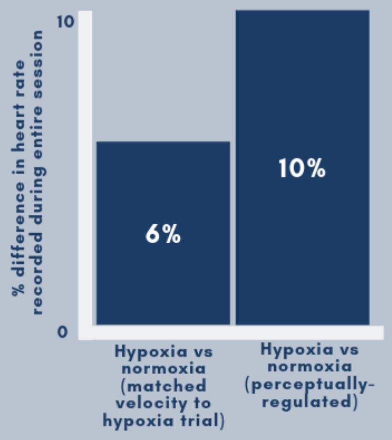
To investigate the acute effects of a 60-min perceptually-regulated (RPE = 14) interval walking (15 x 2/2 mins) session in hypoxic and normoxic conditions, and in normoxia at a matched velocity selected in hypoxia, in obese individuals on physiological responses and exercise-related sensations.

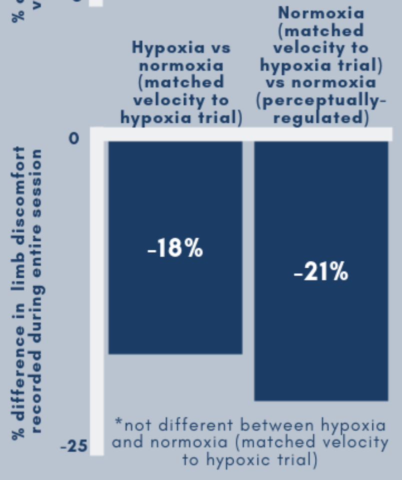
### Methods



### Results







No differences in perceived **recovery**, **motivation**, **breathlessness** and **pleasure** between hypoxia and normoxia

### Conclusions

Obese individuals can achieve a higher internal load (i.e., physiological stress) during perceptually-regulated interval walking in hypoxia at a progressively slower velocity compared to normoxia which is also perceived as less uncomfortable in their legs.

**Created by Liam Hobbins on canva.com**

## 6.2. Abstract

**Aim** Whether perceptually-regulated interval walking session in hypoxia leads to slower walking velocities *versus* normoxia, matches the degree of physiological stress, and preserves exercise-related sensations. Further, whether walking in normoxia at a matched walking velocity selected in hypoxia would produce similar responses in the absence of hypoxia.

**Methods** Ten obese adults (BMI = 32 ± 3 kg/m) completed a 60-min interval session (15 × 2 mins walking/2 mins resting) in hypoxia ($FiO_2$ = 13.0%, $\text{HYP}_{\text{self-selected}}$) and normoxia ($\text{NOR}_{\text{self-selected}}$) at a perceptually-regulated velocity (RPE = 14, 6–20 Borg scale), and in normoxia at the $\text{HYP}_{\text{self-selected}}$ velocity ($\text{NOR}_{\text{imposed}}$).

**Results** Compared to block 1 (6.20 ± 0.02 km/h), velocity was slower during block 4 (6.17 ± 0.06 km/h) and 5 (6.16 ± 0.08 km/h) and in $\text{HYP}_{\text{self-selected}}$ *versus* $\text{NOR}_{\text{self-selected}}$ (6.17 ± 0.04 versus 6.23 ± 0.03 km/h, respectively, $p < 0.05$). Compared to $\text{NOR}_{\text{self-selected}}$ and $\text{NOR}_{\text{imposed}}$, heart rate was higher in $\text{HYP}_{\text{self-selected}}$ (+6 ± 2% and +10 ± 3%, respectively, $p < 0.05$). $SpO_2$ was lower in $\text{HYP}_{\text{self-selected}}$ *versus* $\text{NOR}_{\text{self-selected}}$ and $\text{NOR}_{\text{imposed}}$ (85 ± 1% *versus* 97 ± 0% and 98 ±0%, respectively, $p < 0.01$). Oxyhemoglobin decreased (-3 ± 4%, $p < 0.01$) and deoxyhaemoglobin increased (+28 ± 12%, $p = 0.02$) from block 1 to 5, with larger changes in $\text{HYP}_{\text{self-selected}}$ *versus* $\text{NOR}_{\text{self-selected}}$ (oxyhemoglobin: -4 ± 5%, deoxyhemoglobin: +66 ± 10%) and $\text{NOR}_{\text{imposed}}$ (oxyhemoglobin: -18 ± 31%, deoxyhemoglobin: -65 ± 13%, $p < 0.05$). Perceived limb discomfort was lower in $\text{HYP}_{\text{self-selected}}$ (-21 ± 4%) and $\text{NOR}_{\text{imposed}}$ (-34 ± 6%, $p < 0.05$) *versus* $\text{NOR}_{\text{self-selected}}$. Perceived recovery decreased (-9 ± 2%) and breathlessness increased (+9 ± 1%, $p < 0.05$) from block 1 to 5.

**Conclusions** Perceptually-regulated interval walking in hypoxia at a lower external workload leads to larger physiological stress and lower exercise-related sensations than normoxia, which does not occur in the absence of hypoxia at a matched walking velocity.

## 6.3. Introduction

Walking is an effective, simple strategy to increase the energy expenditure of physical activity and exercise in obese individuals compared to healthy individuals (Browning & Kram, 2005). Just 45–60 mins walking at a fixed-intensity (60% $VO_{2MAX}$), 1–5 times per week for at least six weeks, leads to improvements in total body mass (-5%), systolic blood pressure (-6%), and total (-4%), high- (+6%) and low-density (-4%) cholesterol in obese individuals (Brill et al., 2002, Nicklas et al., 2003). Given the continuous increases in obesity rates across the globe, it seems that current walking programmes are not sufficiently decreasing risk-associated obesity factors as stated previously, and modifications to these strategies are required for achievable health benefits.

Currently, most training programmes employ a pre-determined fixed-intensity of exercise during cycling, based on a '*moderate*' intensity (40–60%) of $VO2_{MAX}$ (Fisher et al., 2015, Kong et al., 2016) or HR reserve (Martins et al., 2015; Shepherd et al., 2015), to be carried out continuously for up to 60 mins per session. Poignant work by Ekkekakis & Lind (2006) showed that an acute bout of self-paced walking (20 mins) increased enjoyment in obese individuals, whereas an intensity imposed that was 10% greater decreased enjoyment levels. Exercise-related sensations (i.e., perceived recovery, motivation, breathlessness, limb discomfort and pleasure) during and following exercise are significant factors for adherence, and importantly, obese individuals are more perceptually sensitive to exercise-induced physiological stress than healthy individuals (Ekkekakis et al., 2016). Therefore, perceptually-regulated (to match an RPE target) walking may be a more appropriate modality for obese individuals than a pre-determined, fixed-intensity. Further, interval exercise (i.e., short periods of work, interspersed with equal, shorter or longer recovery periods) is deemed as time-efficient and leads to positive health outcomes (Gibala et al., 2014). However, no study has addressed the implementation of perceptually-regulated interval exercise in obese individuals specifically, which would likely benefit this population.

Exposure to acute hypoxia during ambulation potentiates slower walking velocities, and maintained metabolic demand compared to normoxic conditions (Girard et al., 2016, Fernandez-Menendez et al., 2018). Further, it is possible to match the acute physiological stress (i.e., HR, muscle oxygenation) accumulated during exercise (60–75% $VO_{2MAX}$ or $HR_{MAX}$ for 60 mins) in hypoxia ($FiO_2$ = 15.0–13.5%) *versus* normoxia for a lower external workload (i.e., power output) (Chacaroun et al., 2018). Study 2 (chapter 5) demonstrated that interval running at a slower velocity in hypoxia (perceptually-regulated to match RPE 16) achieves the same levels of physiological stress (i.e., HR, muscle oxygenation) in normoxia. Whether perceptually-regulated interval walking in obese individuals leads to slower velocities (i.e., lower external workload) in hypoxia compared to normoxia is unknown. This investigation would be advantageous for lowering the external workload to match the internal workload (i.e., physiological stress) in a population at high risk of musculoskeletal injuries (Wearing et al., 2006).

Feelings of overall discomfort increase in a linear fashion alongside increases in BMI (Lecerf et al., 2003). Perceptually-regulated interval walking in hypoxia at a slower walking velocity than normoxia may preserve or alleviate negative exercise-related sensations (Hills et al., 2006), as the external workload will be lower and reduce the physical strain to match an RPE target. In the previous study (chapter 5), it was found that trained runners required a slower perceptually-regulated velocity to match an RPE of 16 during interval running (4 × 4 mins running, 3-min recoveries) but exercise-related sensations were negatively impacted in hypoxia *versus* normoxia. It could be that intervals of a smaller duration, yet more frequently occurring with a lower RPE target would mitigate negative exercise-related sensations, as found previously (Astorino et al., 2019). Whilst exercise training (90 mins combination of resistance and aerobic exercise at 65% peak HR, three sessions per week for 52 weeks) decreases the obesity-dependent declines in cognitive function (Napoli et al., 2014), cognitive function (i.e., central executive and attention) following acute hypoxic exercise is negatively impacted (McMorris et al., 2017). It could also be that cognitive function is maintained following perceptually-regulated interval walking in hypoxia at an expected slower velocity *versus* normoxia due to a lower demand from oxygen-sensing tissues, thought to be a major contributor of cognitive function (Ogoh et al., 2013). If positive exercise-related sensations and cognitive function result from a perceptually-regulated interval walking session at a slower velocity in hypoxia compared to normoxia, it would be of interest to determine whether this is due to hypoxic exposure or a potentially lower external workload. As such, matching the velocity selected in hypoxia and carrying this out in normoxia would isolate the therapeutic potential of hypoxia *per se* in obese individuals during perceptually-regulated interval walking. Therefore, the aim of this study was to investigate the acute effect of a 60-min perceptually-regulated (RPE = 14) interval walking (2/2 mins) session in hypoxic and normoxic conditions in obese individuals on physiological/metabolic responses, as well as exercise-related sensations and cognitive function. The interval/rest duration selected here is based upon the findings of study 1 (chapter 4) of the current thesis. It was hypothesised that walking velocity would become progressively slower in hypoxic conditions compared to normoxia, which would lead to similar levels of physiological (except $SpO_2$) and metabolic stress, whilst adjustments in exercise-related sensations and cognitive function would be matched. Further, when the velocity selected by participants in hypoxia is replicated in normoxia and compared to self-selected walking speeds in normoxia, lower physiological and metabolic stress as well as similar exercise-related sensations and cognitive function would arise.

## 6.4. Methods

### 6.4.1. Participants

Ten obese (7 males, 3 females; age: 38.2 ± 11.9 years; height: 171 ± 10 cm; weight: 93.8 ± 10.1 kg; BMI: 32.1 ± 2.8 kg/m) individuals participated in this study after meeting the eligibility criteria and providing written informed consent. This study received ethical approval from the School of Applied Science, LSBU (SAS1725).

### 6.4.2. Experimental design

Participants attended the laboratory on four separate occasions. The first session consisted of eligibility determination, familiarisation with the measures and treadmill walking, and identification of preferred walking velocity. Within 72 h, participants returned to the lab for the first of three experimental trials, each separated by seven days to enable a washout period (Kelly & Basset, 2017). Participants completed a 60-min interval session (15 × 2 mins walking, 2 mins resting) during each experimental trial; once in hypoxia at a perceptually-regulated (RPE = 14) velocity ($FiO_2$ = 13.0%, equivalent to ~3500 m elevation above sea level; $HYP_{self\text{-}selected}$), in normoxia at a perceptually-regulated velocity ($NOR_{self\text{-}selected}$), and in normoxia at the velocity self-selected in the hypoxic trial ($NOR_{imposed}$). The interval duration (2/2 mins) selected in the current study was based upon the findings of study 1 (chapter 4), whereby, obese individuals perceived shorter cycles of passive hypoxic conditioning as more tolerable yet received similar levels of desaturation. Each interval session was followed by a 60-min recovery period in normoxia. The first and second experimental trials corresponded to perceptually-regulated hypoxic and normoxic interval sessions, performed in a randomised order, whilst the third trial was the imposed velocity from $HYP_{self\text{-}selected}$ in normoxic conditions. Velocity, physiological (HR, $SpO_2$ and muscle oxygenation) and perceptual (recovery, motivation, breathlessness, limb discomfort and pleasure) responses were measured during the interval walking session. Cognitive function (accuracy and reaction time), metabolic

(EE, RER and substrate utilisation) and perceptual responses (affect and exercise self-efficacy) were measured before and after (up to 60 min) the interval walking session.

### *6.4.3. Familiarisation session*

Participants were firstly familiarised with the perceptual scales, cognitive test and walking on the treadmill (Pulsar, h/p/cosmos, Germany). Secondly, preferred walking velocity was determined (3.7.). After 10 mins of rest, participants completed one 2-min interval composing the interval walking protocol (see below) for habituation.

### *6.4.4. Experimental trials*

After a standardised 5-min warm up at 3.0 km/h, a facemask connected to a portable hypoxic generator (3.8.) was attached to the participants. Participants completed 15, 2-min intervals, each separated by 2 mins of passive recovery (quiet standing). The first 30 s of each 2-min interval began at participants' pre-determined, perceptually-regulated walking velocity (RPE = 14) during all sessions. During the perceptually-regulated trials in hypoxia and normoxia, participants were free to decide if and how treadmill velocity needed to be altered (i.e., self-paced and adjusted manually by the investigator) to ensure maintenance of an RPE of 14 whilst walking every 30 s (3.7.). The velocity selected by participants during the hypoxic condition was matched and imposed during interval walking in normoxia to isolate the effects of hypoxia, which was always scheduled as the final experimental trial.

### *6.4.5. Hypoxic conditioning*

Participants wore a facemask (Altitude Training Mask, Hypoxico Altitude Training Systems, USA) connected *via* corrugated plastic tubing to a hypoxic generator (Everest Training Summit II, Hypoxico Altitude Training Systems, USA) to create hypoxic conditions (3.8.). The $FiO_2$ provided in this study was 13.0% (simulated altitude of ~3500 m), deemed safe in the population studied (Navarrete-Opazo & Mitchell, 2014). Total hypoxic exposure corresponded to exactly 60 mins with the facemask remaining attached during the $HYP_{self-paced}$ walking session.

### *6.4.6. Measures*

### *6.4.6.1. During interval walking session*

Treadmill velocity, HR (3.9.1.) and $SpO_2$ (3.9.2.) were manually recorded every 30 s during each 2-min interval.

Muscle oxygenation trends of the *vastus lateralis* muscle were recorded using near-infrared spectroscopy (NIRS; NIRO-2000NX, Hamamatsu, Japan) in real-time (3.9.4.). Bi-polar optode sensors were attached approximately 10 cm above the proximal border of the patella *via* double-sided adhesive tape and housed (3 cm apart, 775 Nm wavelength) within rubber-cased hoods.

Perceived recovery (3.11.1.) and motivation to exercise (3.11.2.) were assessed 30 s before each 2-min interval. Recovery was assessed before the first interval to determine perceptions following the warm up. Immediately after each 2-min interval, ratings of perceived breathlessness (3.11.3.), limb discomfort (3.11.4.) and pleasure (3.11.5.) were assessed.

### *6.4.6.2. Pre- and post-walking*

Participants sat quietly during the recovery period. Expired gas samples (5-min) were collected at baseline and 0 (Post0), 30 (Post30) and 60 (Post60) mins after interval walking for assessment of EE, RER and fuel utilisation (3.10.1.).

Perceived mood state (3.11.6.), PANAS (3.11.7.) and exercise self-efficacy (3.11.8.) were assessed at baseline and immediately (Post0), 30 (Post30) and 60 (Post60) mins after the interval walking session.

Cognitive function was assessed at baseline, 0 (Post0) and 60 (Post60) mins after interval walking *via* the *n*-back task (3.12.2.).

### *6.4.7. Data analysis*

Data were processed offline into Excel (Microsoft Office, 2016). HR and $SpO_2$ values were averaged across each 2-min interval. Muscle oxygenation and expired gas parameters were smoothed using a 5-point moving average. For muscle oxygenation, the last 30 s of each 2-min walking interval and 2-min rest period were averaged and normalized to the 30-s rest period before the first interval (reference values) for each respective condition and then presented as absolute ([$O_2$Hb], [HHb] and [tHb]) and percentage (TSI) change (Chacaroun et al., 2018). For expired gas, the first and last 30 s of each 5-min sample were removed to nullify any fluctuations with measurement initiation/cessation and anticipation of mask removal (Workman & Basset, 2012). All perceptual data are expressed as raw values due to there being no significant differences at baseline. Target and non-target accuracy and reaction time were averaged across the cognitive task and calculated as percentage difference from baseline. Velocity, HR, $SpO_2$, muscle oxygenation and perceptual measures assessed during the interval walking session were condensed by averaging intervals into five blocks of three (i.e., block 1: 1–3, block 2: 4–6, block 3: 7–9, block 4: 10–12 and block 5: 13–15).

### *6.4.8. Statistical analysis*

A two-way ANOVA was used to investigate the main effect of condition ($HYP_{self\text{-}selected}$ *versus* $NOR_{self\text{-}selected}$ and $NOR_{imposed}$), time (baseline *versus* Post0, Post30 and Post60 or block 1 *versus* 2, 3, 4 and 5) and the condition × time interaction.

## 6.5. Results

### *6.5.1. During interval walking session*

#### *6.5.1.1. Velocity*

Participants adjusted to a slower velocity during block 4 and 5 and more so in $\text{HYP}_{\text{self-selected}}$ *versus* $\text{NOR}_{\text{self-selected}}$ compared to block 1 (-1.7 ± 0.1% and -2.2 ± 0.2%, respectively, $p < 0.05$, Figure 6.1.A). The velocity during $\text{NOR}_{\text{imposed}}$ was lower than $\text{NOR}_{\text{self-selected}}$ (-1.7 ± 0.1% and -2.2 ± 0.2%, respectively, $p < 0.05$, Figure 6.1.A) but not different to $\text{HYP}_{\text{self-selected}}$ ($p > 0.05$).

#### *6.5.1.2. Heart rate & $SpO_2$*

HR increased progressively from block 1 to 5 (+5.0 ± 0.5%, $p = 0.01$, Figure 6.1.B). Compared to $\text{NOR}_{\text{self-selected}}$ and $\text{NOR}_{\text{imposed}}$, HR was higher overall during $\text{HYP}_{\text{self-selected}}$ (+5.7 ± 1.0% and +10.0 ± 2.3%, respectively, $p < 0.05$). $SpO_2$ was lower throughout $\text{HYP}_{\text{self-selected}}$ (84.6 ± 0.8%) *versus* $\text{NOR}_{\text{self-selected}}$ (97.3 ± 0.2%, $p < 0.01$) and $\text{NOR}_{\text{imposed}}$ (97.7 ± 0.3%, $p < 0.01$, Figure 6.1.C).

#### *6.5.1.3. Muscle oxygenation*

[$O_2$Hb] during exercise (-6.31 ± 0.40 Δμmol, $p < 0.01$, Figure 6.2.A) and rest (-5.47 ± 0.61 Δμmol, $p < 0.01$, Figure 6.2.B) decreased progressively from block 1 to 5, and more so in $\text{HYP}_{\text{self-selected}}$ *versus* $\text{NOR}_{\text{imposed}}$ (exercise [$O_2$Hb]: -2.38 ± 1.05 Δμmol, $p = 0.05$, rest [$O_2$Hb]: -3.94 ± 1.77 Δμmol, $p < 0.01$). Compared to $\text{NOR}_{\text{self-selected}}$, [$O_2$Hb] during rest decreased progressively during $\text{HYP}_{\text{self-selected}}$ (-3.36 ± 0.46 Δμmol, $p = 0.02$) but not $\text{NOR}_{\text{imposed}}$ ($p > 0.05$). [HHb] during exercise increased progressively from block 1 to 5 (+1.1 ± 0.98 Δμmol, $p = 0.02$, Figure 6.2.C), and more so during $\text{HYP}_{\text{self-selected}}$ *versus* $\text{NOR}_{\text{self-selected}}$ and $\text{NOR}_{\text{imposed}}$ (+4.21 ± 0.70 and +3.50 ± 1.27 Δμmol, respectively). [HHb] during rest was larger in $\text{HYP}_{\text{self-selected}}$ *versus* $\text{NOR}_{\text{self-selected}}$ and $\text{NOR}_{\text{imposed}}$, and from block 1 to 5 (+3.87 ± 0.32 and +3.00 ± 0.91 Δμmol, respectively, $p < 0.01$, Figure 6.2.D). [tHb] during exercise decreased from block

1 to 5 (+0.02 ± 0.01 Δμmol, $p = 0.02$, Figure 6.2.E), irrespective of condition ($p = 0.24$). [tHb] during rest was unaffected over time and between conditions ($p > 0.05$, Figure 6.2.F). TSI during exercise (-2.7 ± 1.3%, $p < 0.01$, Figure 6.3.A) and rest (-3.2 ± 2.1%, $p < 0.01$, Figure 6.3.B) decreased progressively from block 1 to 5, and more so in $\text{HYP}_{\text{self-selected}}$ *versus* $\text{NOR}_{\text{self-selected}}$ and $\text{NOR}_{\text{imposed}}$ (exercise TSI: -5.9 ± 0.7% and -5.5 ± 0.2%, respectively, rest TSI: -5.6 ± 0.8% and -5.2 ± 0.6%, respectively, all $p < 0.01$).

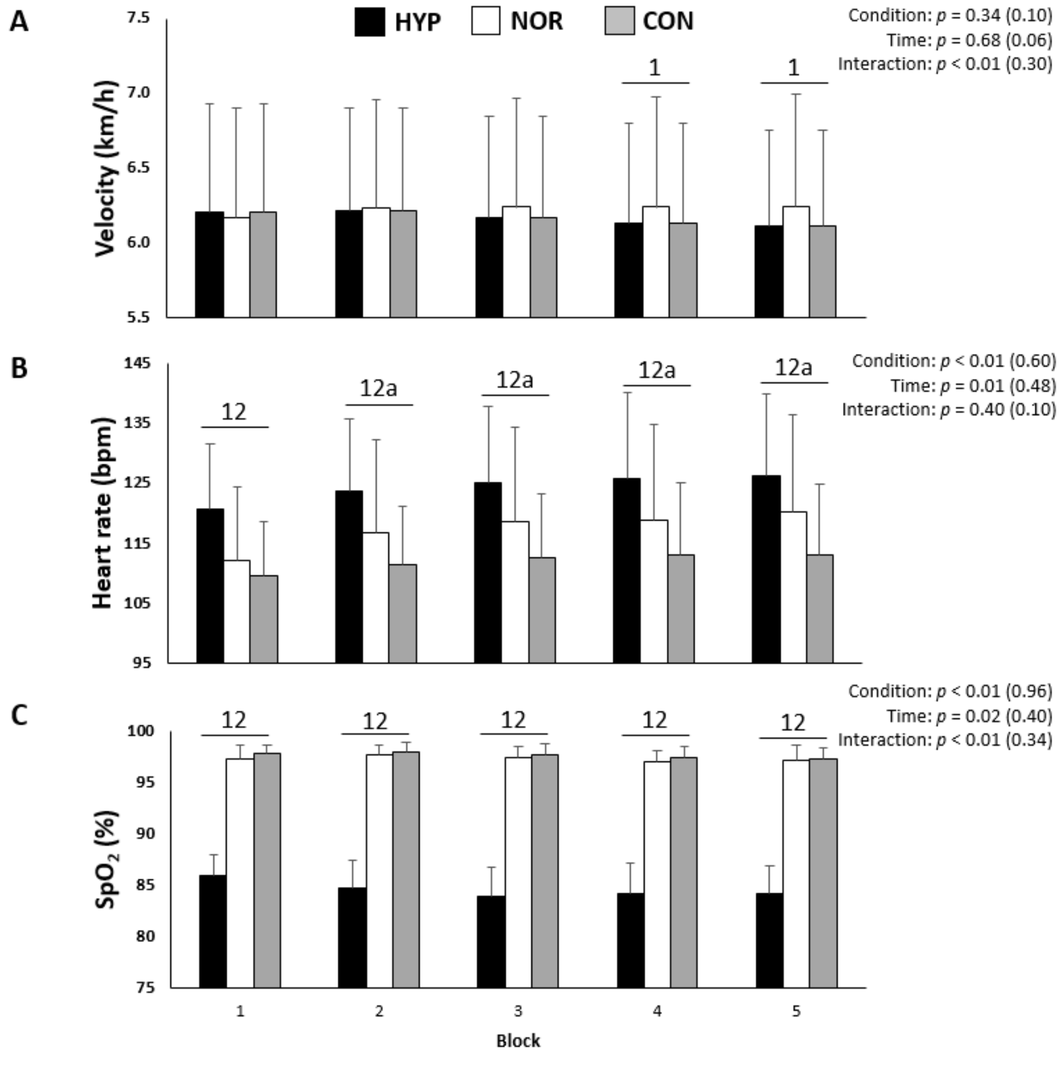


**Figure 6.1.** Changes in velocity (A), heart rate (B) and arterial oxygen saturation ($SpO_2$; C) during the interval walking session. Data are condensed into five blocks for every three 2-min intervals and presented as mean ± SD. ANOVA main effects of time, condition and interaction are stated along with partial-eta squared for effect size into brackets. Black bars = self-paced hypoxic condition ($\text{HYP}_{\text{self-selected}}$); white bars = self-paced normoxic condition ($\text{NOR}_{\text{self-selected}}$); grey bars = normoxic condition imposed with velocity selected in hypoxic condition ($\text{NOR}_{\text{imposed}}$). 1 and 2 denotes a statistically significant difference ($p < 0.05$) between $\text{HYP}_{\text{self-selected}}$ *versus* $\text{NOR}_{\text{self-selected}}$ and $\text{NOR}_{\text{imposed}}$, respectively. a denotes a statistically significant difference ($p < 0.05$) compared to block 1.

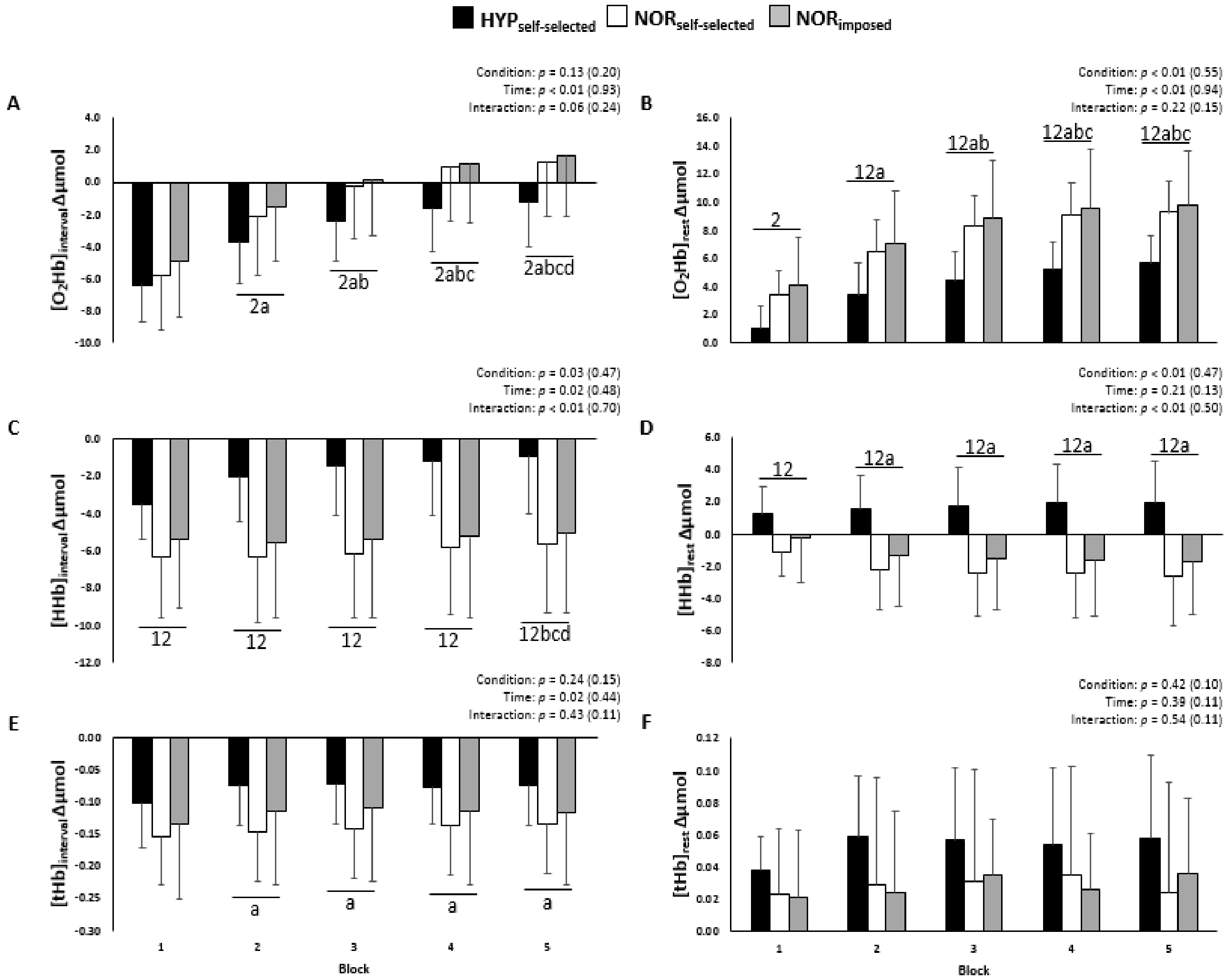


**Figure 6.2.** Changes in oxyhemoglobin ($O_2$Hb; A–B), deoxyhemoglobin (HHb; C–D) and total haemoglobin (tHb; E–F) parameters of the vastus lateralis muscle during the interval walking session. Data are condensed into five blocks for every three 2-min intervals and rest periods, and presented as mean ± SD. ANOVA main effects of time, condition and interaction are stated along with partial-eta squared for effect size into brackets. Black bars = self-paced hypoxic condition ($HYP_{self\text{-}selected}$); white bars = self-paced normoxic condition ($NOR_{self\text{-}selected}$); grey bars = normoxic condition imposed with velocity selected in hypoxic condition ($NOR_{imposed}$). 1 and 2 denotes a statistically significant difference ($p < 0.05$) between $HYP_{self\text{-}selected}$ *versus* $NOR_{self\text{-}selected}$ and $NOR_{imposed}$, respectively. a, b, c and d denotes a statistically significant difference ($p < 0.05$) compared to block 1, 2, 3 and 4, respectively.

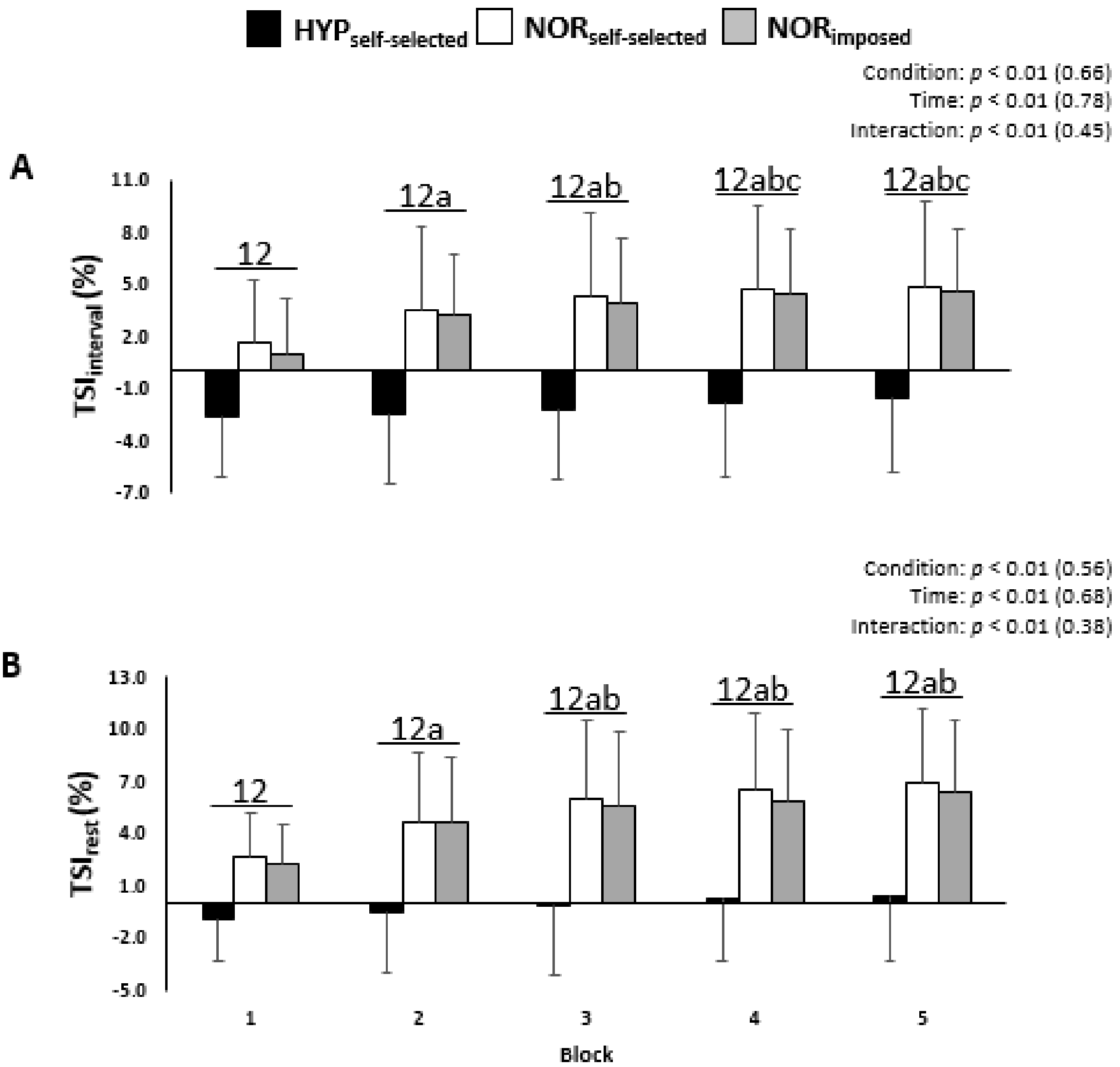


**Figure 6.3.** Changes in tissue saturation index (TSI) of the vastus lateralis muscle during walking (A) and rest (B) of the interval walking session. Data are condensed into five blocks for every three 2-min intervals and rest periods, and presented as mean ± SD. ANOVA main effects of time, condition and interaction are stated along with partial-eta squared for effect size into brackets. Black bars = self-paced hypoxic condition ($HYP_{self\text{-}selected}$); white bars = self-paced normoxic condition ($NOR_{self\text{-}selected}$); grey bars = normoxic condition imposed with velocity selected in hypoxic condition ($NOR_{imposed}$). 1 and 2 denotes a statistically significant difference ($p < 0.05$) between $HYP_{self\text{-}selected}$ *versus* $NOR_{self\text{-}selected}$ and $NOR_{imposed}$, respectively. a, b and c denotes a statistically significant difference ($p < 0.05$) compared to block 1, 2 and 3, respectively.

### *6.5.1.4. Perceptual responses*

Perceived recovery decreased progressively from block 1 to 5 (-11 ± 1%, $p < 0.01$, Figure 6.4.A), irrespective of condition ($p > 0.05$). Perceived motivation was unaffected over time and between conditions ($p > 0.05$, Figure 6.4.B). Perceived breathlessness increased progressively from block 1 to 5 (+9 ± 1%, $p < 0.01$, Figure 6.4.C), irrespective of condition ($p > 0.05$). Perceived limb discomfort was lower overall during $\text{HYP}_{\text{self-selected}}$ (-18 ± 3%, $p = 0.03$, Figure 6.4.D) and $\text{NOR}_{\text{imposed}}$ (-21 ± 6%, $p = 0.06$) *versus* $\text{NOR}_{\text{self-selected}}$, irrespective of time. Perceived pleasure was unaffected over time and between conditions ($p > 0.05$, Figure 6.4.E).

### *6.5.2. Pre- and post-walking*

#### *6.5.2.1. Metabolism*

There was no effect of time and condition on EE ($\text{HYP}_{\text{self-selected}}$: 1.70 ± 0.08 kcal/min, $\text{NOR}_{\text{self-selected}}$: 1.66 ± 0.08 kcal/min, $\text{NOR}_{\text{imposed}}$: 1.66 ± 0.05 kcal/min, $p > 0.05$). RER decreased from baseline (0.75 ± 0.01) to Post0 (0.72 ± 0.04), Post30 (0.70 ± 0.02) and Post60 (0.71 ± 0.01; $p < 0.01$, Figure 6.5.A). RER at Post0 and Post30 was lower in $\text{HYP}_{\text{self-selected}}$ (0.67 ± 0.07 and 0.67 ± 0.06, respectively) compared to $\text{NOR}_{\text{self-selected}}$ (Post0: 0.74 ± 0.06, Post30: 0.71 ± 0.07) and $\text{NOR}_{\text{imposed}}$ (Post0: 0.74 ± 0.07, Post30: 0.71 ± 0.07). Fat metabolism was higher at Post0 (1.41 ± 0.14 kcal/min), Post30 (1.49 ± 0.10 kcal/min) and Post60 (1.34 ± 0.06 kcal/min) compared to baseline (1.27 ± 0.03 kcal/min; $p < 0.01$, Figure 6.5.B), irrespective of condition. Glucose metabolism was lower at Post0 (0.24 ± 0.11 kcal/min), Post30 (0.17 ± 0.06 kcal/min) and Post60 (0.18 ± 0.01 kcal/min) compared to baseline (0.33 ± 0.01 kcal/min; $p < 0.07$, Figure 6.5.C), irrespective of condition.

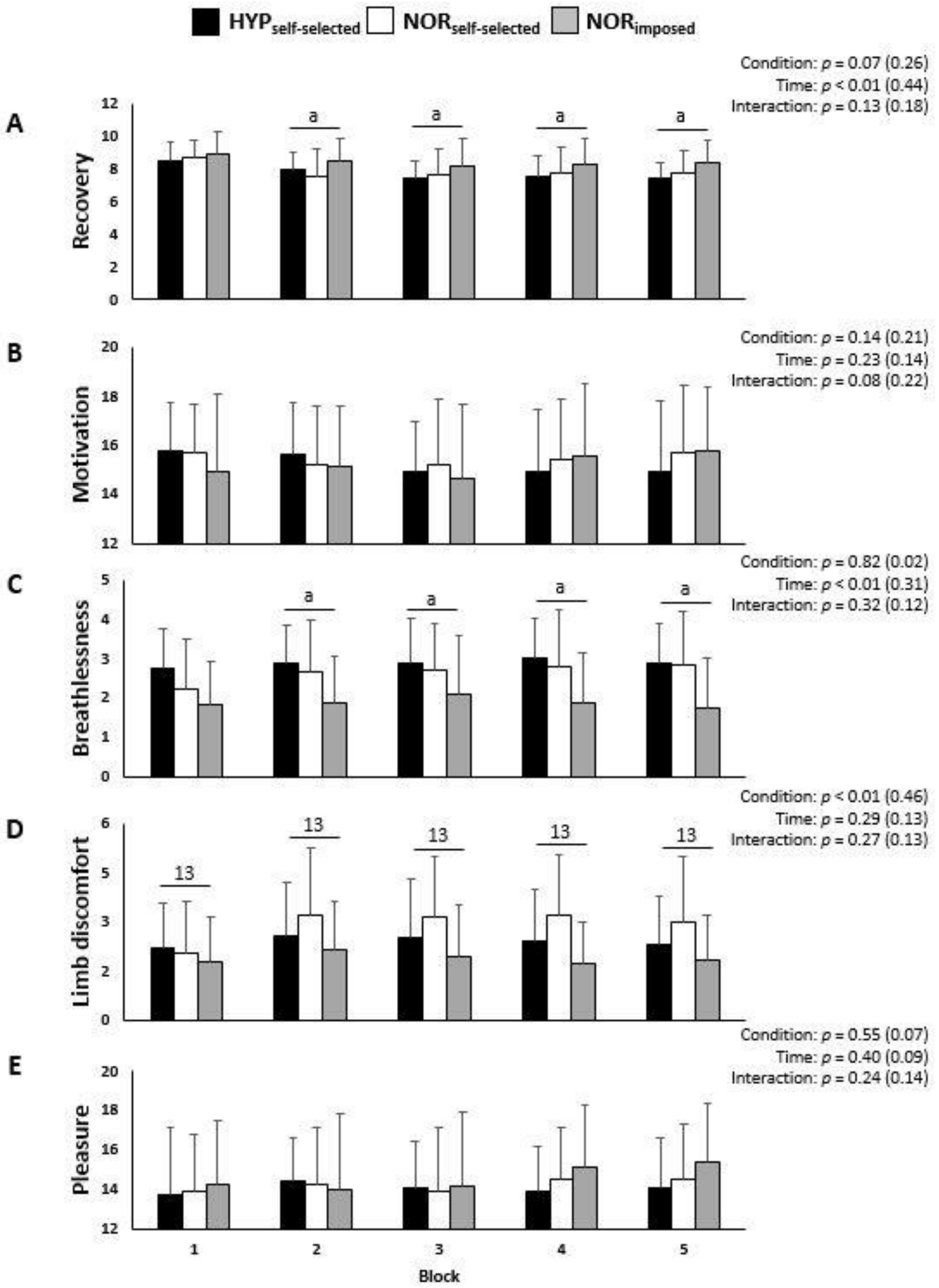


**Figure 6.4.** Changes in perceived recovery (A), motivation (B), breathlessness (C), limb discomfort (D) and pleasure (E) during the interval walking session. Data are condensed into five blocks for every three 2-min intervals and rest periods, and presented as mean ± SD. ANOVA main effects of time, condition and interaction are stated along with partial-eta squared for effect size into brackets. Black bars = self-paced hypoxic condition ($HYP_{self\text{-}selected}$); white bars = self-paced normoxic condition ($NOR_{self\text{-}selected}$); grey bars = normoxic condition imposed with velocity selected in hypoxic condition ($NOR_{imposed}$). 1 and 3 denotes a statistically significant difference ($p < 0.05$) for $HYP_{self\text{-}selected}$ *versus* $NOR_{self\text{-}selected}$ and $NOR_{imposed}$ *versus* $NOR_{self\text{-}selected}$, respectively. a denotes a statistically significant difference ($p < 0.05$) compared to block 1.

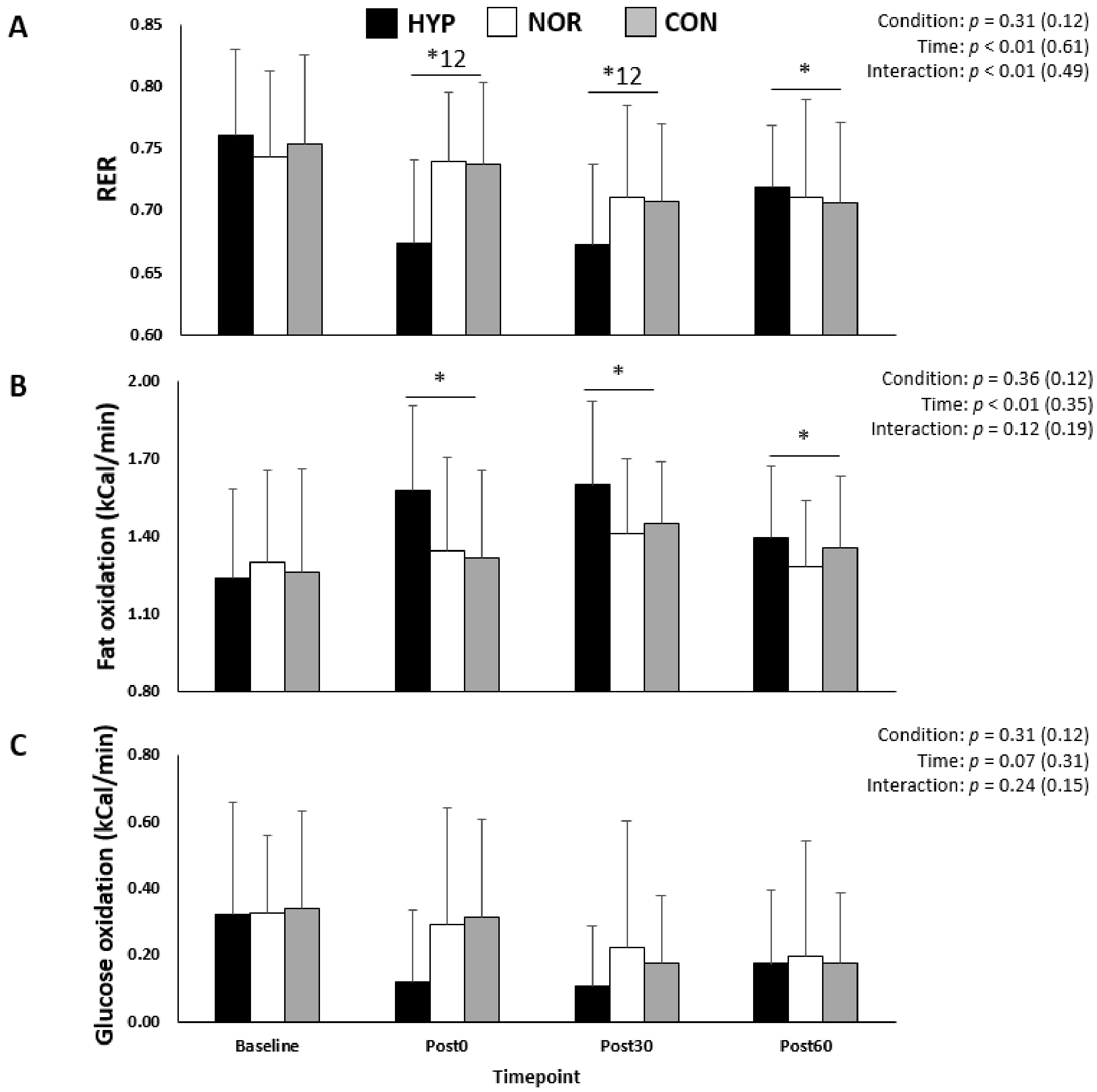


**Figure 6.5.** Changes in respiratory exchange ratio (RER; A), fat (B) and glucose oxidation (C) assessed at baseline and 0 (Post0), 30 (Post30) and 60 (Post60) mins after the interval walking session. Data are presented as mean ± SD. ANOVA main effects of time, condition and interaction are stated along with partial-eta squared for effect size into brackets. Black bars = self-paced hypoxic condition ($HYP_{self\text{-}selected}$); white bars = self-paced normoxic condition ($NOR_{self\text{-}selected}$); grey bars = normoxic condition imposed with velocity selected in hypoxic condition ($NOR_{imposed}$). 1 and 2 denotes a statistically significant difference ($p < 0.05$) between $HYP_{self\text{-}selected}$ *versus* $NOR_{self\text{-}selected}$ and $NOR_{imposed}$, respectively. * and # denotes a statistically significant difference ($p < 0.05$) and trend ($p < 0.07$), respectively, compared to baseline.

### *6.5.2.2. Perceptual responses*

Perceived mood state increased over time (+26 ± 7%, $p = 0.02$, Figure 6.6.A), irrespective of condition. Positive affect was lower at Post0 (-7 ± 1%), Post30 (-1 ± 0%) and Post60 (-4 ± 2%) compared to baseline ($p = 0.02$, Figure 6.6.B). At Post0 and Post30, positive affect was lower in $\text{HYP}_{\text{self-selected}}$ compared to $\text{NOR}_{\text{self-selected}}$ (Post0: -11 ± 6%, Post30: -6 ± 0%) and $\text{NOR}_{\text{imposed}}$ (Post0: -10 ± 1%, Post30: -1 ± 2%, $p < 0.01$, Figure 6.6.B). Negative affect decreased over time (-7 ± 2%, $p = 0.04$, Figure 6.6.D), but pairwise comparisons were unable to identify at which point of measurement. Exercise self-efficacy was lower at Post0 after $\text{HYP}_{\text{self-selected}}$ *versus* $\text{NOR}_{\text{self-selected}}$ (-25 ± 5%, $p < 0.05$, Figure 6.6.C).

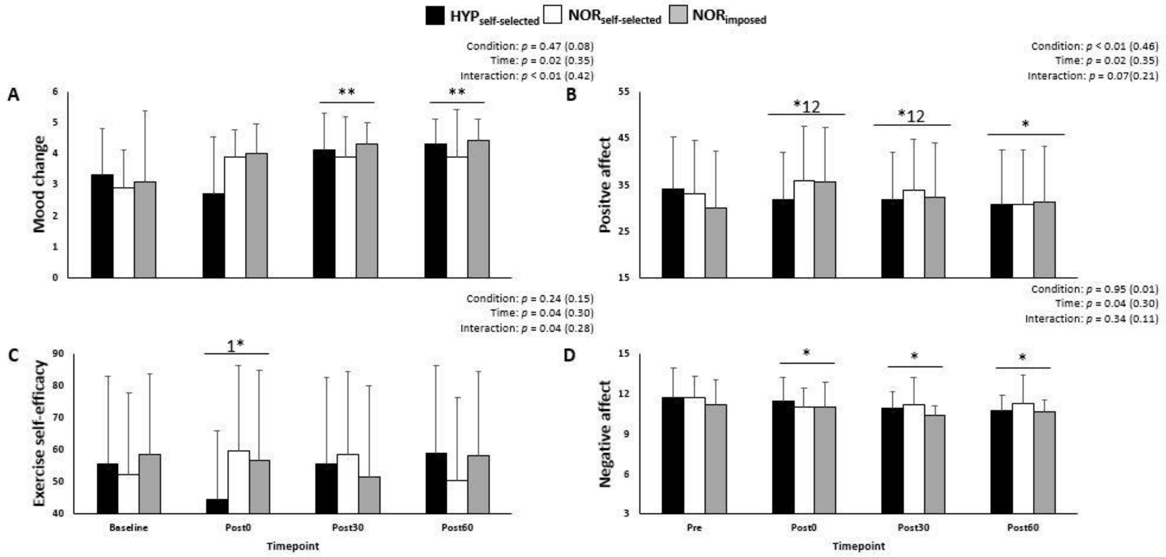


**Figure 6.6.** Changes in perceived mood change (A), positive affect (B), exercise self-efficacy (C) and negative affect (D) assessed at baseline and 0 (Post0), 30 (Post30) and 60 (Post60) mins after the interval walking session. Data are presented as absolute change from baseline and as mean ± SD. ANOVA main effects of time, condition and interaction are stated along with partial-eta squared for effect size into brackets. Black bars = self-paced hypoxic condition ($\text{HYP}_{\text{self-selected}}$); white bars = self-paced normoxic condition ($\text{NOR}_{\text{self-selected}}$); grey bars = normoxic condition imposed with velocity selected in hypoxic condition ($\text{NOR}_{\text{imposed}}$). 1 and 2 denotes a statistically significant difference ($p < 0.05$) between $\text{HYP}_{\text{self-selected}}$ *versus* $\text{NOR}_{\text{self-selected}}$ and $\text{NOR}_{\text{imposed}}$, respectively. * and ** denotes a statistically significant difference ($p < 0.05$) compared to baseline and post0, respectively.

### *6.5.2.3. Cognitive function*

Compared to $\text{NOR}_{\text{self-selected}}$, non-target accuracy was lower following $\text{NOR}_{\text{imposed}}$ at Post0 (-6.7 ± 1.5%, $p = 0.01$, Figure 6.7.C). Target accuracy (Figure 6.7.A), target reaction time (Figure 6.7.B) and non-target reaction time (Figure 6.7.D, all $p > 0.05$) were unaffected over time and between conditions.

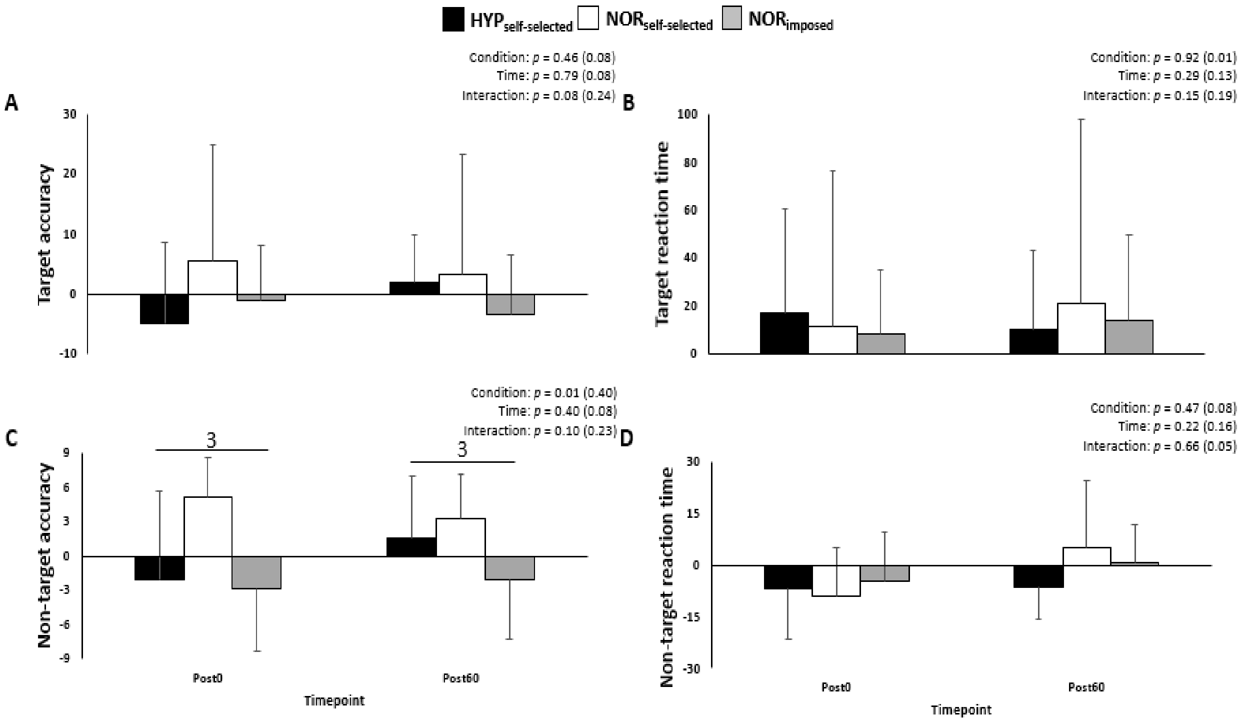


**Figure 6.7.** Changes in target accuracy (A) and reaction time (B) and non-target accuracy (C) and reaction time (D) assessed at baseline, 0 and 30 mins after the interval walking session. Data are presented as percentage difference from baseline and as mean ± SD. ANOVA main effects of time, condition and interaction are stated along with partial-eta squared for effect size into brackets. Black bars = self-paced hypoxic condition ($\text{HYP}_{\text{self-selected}}$); white bars = self-paced normoxic condition ($\text{NOR}_{\text{self-selected}}$); grey bars = normoxic condition imposed with velocity selected in hypoxic condition ($\text{NOR}_{\text{imposed}}$). 3 denotes a statistically significant difference ($p < 0.05$) between $\text{NOR}_{\text{self-selected}}$ *versus* $\text{NOR}_{\text{imposed}}$.

## 6.6. Discussion

The aim of the present study was to investigate whether perceptually-regulated (RPE = 14) interval walking in hypoxia leads to slower walking velocities for equivalent physiological and metabolic responses, exercise-related sensations and cognitive function in normoxia; and in the absence of hypoxia, whether these responses will be maintained at a matched velocity. The main findings show that a slower walking velocity is adopted towards the end of $HYP_{self\text{-}selected}$ compared with $NOR_{self\text{-}selected}$, with a greater physiological stress (i.e., higher HR, lower $SpO_2$ and muscle oxygenation) in the former than the latter. For a matched velocity of $HYP_{self\text{-}selected}$ in normoxia, less physiological stress is present. Participants felt less discomfort in their lower limbs throughout interval walking in $HYP_{self\text{-}selected}$ and $NOR_{imposed}$ compared to $NOR_{self\text{-}selected}$. A lower RER, positive affect and exercise self-efficacy were recorded after $HYP_{self\text{-}selected}$ for up to 30 mins *versus* $NOR_{self\text{-}selected}$ and $NOR_{imposed}$. Cognitive function (i.e., non-target accuracy) was maintained following $HYP_{self\text{-}selected}$ but lower after $NOR_{imposed}$ compared to $NOR_{self\text{-}selected}$. Overall, perceptually-regulated interval walking in hypoxia at a lower external workload (i.e., walking velocity) achieves a higher physiological stress for a lower perceived load (i.e., limb discomfort) compared to normoxia, but not in the absence of hypoxia at a matched intensity.

### *6.6.1. During interval walking session*

Throughout $HYP_{self\text{-}selected}$, greater physiological stress (i.e., higher HR, lower $SpO_2$ and muscle oxygenation) was present compared to $NOR_{self\text{-}selected}$ and $NOR_{imposed}$. These findings are somewhat different to the previous chapter (study 2, chapter 6), whereby there were no differences in HR and muscle oxygenation parameters during perceptually-regulated interval running (4 × 4 mins running at RPE = 16, 3-min recoveries) between hypoxia ($FiO_2$ = 15.0%) and normoxia. This may partly be due to larger adjustments in workload (i.e., decreased treadmill velocity) found in the previous (-6%) than the current study (-1%) during hypoxic conditioning. Slower hypoxia-induced walking velocities for a given exercise intensity (i.e., RPE or HR target) may have subsequently preserved levels of physiological stress, as shown previously during 60-min continuous running/walking (Wiesner et al., 2010) and interval (15 × 1/1-min) cycling (Chacaroun et al., 2018). Interestingly, in normoxia at a matched walking velocity self-selected in hypoxia ($NOR_{imposed}$), physiological stress levels were lower (i.e., lower HR, higher $SpO_2$ and muscle oxygenation) during the current study. It has been shown that obese individuals are unable to achieve the chronic physiological adaptations (i.e., aerobic capacity, skeletal muscle oxidative capacity and cardiovascular function) required for improvements in health during fixed-intensity interval cycling (10 × 1/1-min, 100% peak aerobic power) in normoxia (Boyd et al., 2013). Albeit from an acute study, the present data supports the notion that walking at a slightly slower velocity in hypoxia than normoxia may be useful to obtain the necessary physiological adaptations from exercise. Further, the exercise intensity employed here was perceptually-regulated by the participants which is regarded as more enjoyable than imposed intensities (Ekkekakis & Lind, 2006). Therefore, the positive physiological responses achieved during interval walking in $HYP_{self\text{-}selected}$ are likely accompanied with perceptual benefits (i.e., more enjoyment). Overall, perceptually-regulated interval walking in hypoxia leads to greater levels of physiological stress compared to higher or matched workloads in normoxia.

Decreased perceptions of lower limb discomfort were found throughout $HYP_{self\text{-}selected}$ compared with $NOR_{self\text{-}selected}$ and $NOR_{imposed}$. The decreases recorded during $HYP_{self\text{-}selected}$ also occurred prior to participants lowering the treadmill velocity to maintain an RPE of 14 during interval walking. The current data suggests that when walking in hypoxia ($FiO_2 = 13.0\%$) at a perceptually-regulated intensity, there may be a potential disconnection between overall RPE and the contribution of perceived limb discomfort to an RPE target of 14, that is not present when in normoxia (Abbiss et al., 2015). However, when the velocity selected in hypoxia is matched in normoxic conditions, perceived limb discomfort is inferior to that felt at a perceptually-regulated intensity in normoxia. As such, slower walking velocities rather than hypoxic exposure leads to lower perceived limb discomfort in obese individuals. This is unlike the findings of Christian et al. (2014), whom found greater perceived limb discomfort during 5 mins continuous, sub-maximal, perceptually-regulated (RPE 3 on Borg CR10 scale) cycling in hypoxia ($FiO_2$ = 13.5%) *versus* normoxia. Interestingly, the time-dependent changes in perceived recovery (decreased) and breathlessness (increased) did not differ between conditions, whilst perceived motivation and pleasure were maintained during perceptually-regulated interval walking. In summary, a slower perceptually-regulated walking velocity in hypoxia leads to decreased perceived limb discomfort compared to normoxia.

### *6.6.2. Pre- and post-walking*

Following $HYP_{self\text{-}selected}$, a lower RER was recorded up to 30 mins after interval walking compared to $HYP_{self\text{-}selected}$ and $NOR_{imposed}$. As described by Henderson et al. (2007), this is likely explained through carbon dioxide retention following intense exercise that typically lasts for up to 60 mins whilst bicarbonate stores are replenished. In the current study, fat metabolism was lower whilst glucose metabolism was higher for up to 60 mins after interval walking, irrespective of condition. Kelly and Basset (2017) reported more pronounced increases in fat metabolism and decreases in glucose metabolism following 60 mins continuous, fixed-intensity (50% peak power output) cycling in hypoxia ($FiO_2$ = 15.0%) compared to normoxia in healthy males. Although similar time effects on post-exercise fuel metabolism compared to baseline were found in the aforementioned and present study, the present findings may not have differed between conditions due to the total duration of exercise (60 *versus* 30 mins, respectively). A greater total exercise duration may have led to larger metabolic stress compared with a shorter total exercise duration (Hildebrandt et al., 2003). This may explain the absence of a time or condition effect on EE – whereby, the results of the present study show that there is no effect on resting EE following perceptually-regulated interval walking in hypoxia or normoxia at a perceptually-regulated or imposed intensity. To conclude, although a lower RER is recorded for up to 30 mins after perceptually-regulated interval walking in hypoxia compared to normoxia, similar increases in fat and decreases in glucose oxidation are realised independent of condition.

Positive affect and exercise self-efficacy were lower for up to 30 mins after $HYP_{self\text{-}selected}$ compared with $NOR_{self\text{-}selected}$ and $NOR_{imposed}$. This is somewhat in disagreement with the proposed hypothesis, which postulated matched exercise-related sensations between perceptually-regulated interval walking at a slower velocity in hypoxia *versus* normoxia, whilst exercise-related sensation would be greater in $NOR_{imposed}$. Lower ratings of positive affect and exercise self-efficacy following $HYP_{self\text{-}selected}$ may be explained through the larger physiological stress experienced during interval walking compared to $NOR_{self\text{-}selected}$ and $NOR_{imposed}$. Overweight individuals are considered to be more perceptually sensitive to exercise-induced physiological stress than healthy individuals (Ekkekakis et al., 2016). As such, it could be argued that if earlier and greater adjustments (i.e., decreases) to interval walking velocity during $HYP_{self\text{-}selected}$ were made compared with $NOR_{self\text{-}selected}$ leading to matched exercise-induced physiological stress, exercise-related sensations would be preserved after interval walking in the current study. However, time-dependent increases in perceived mood change and decreased negative affect occurred despite the effect of interval walking velocity or environmental condition. This is likely due to the positive effect of acute exercise on mood change, irrespective of intensity (Meyer et al., 2016). In summary, despite the decreases in interval walking velocity during $HYP_{self\text{-}selected}$, exercise-related sensations are negatively impacted for upto 30 mins after compared with $NOR_{self\text{-}selected}$ and $NOR_{imposed}$.

Cognitive function was maintained following $HYP_{self\text{-}selected}$ compared to $NOR_{self\text{-}selected}$ and $NOR_{imposed}$, whilst non-target accuracy was lower following $NOR_{imposed}$ compared to $NOR_{self\text{-}selected}$ for upto 60 mins. It has been reported that exercise in hypoxia negatively impacts cognitive function, likely due to decreased $SpO_2$ compared to normoxia (de Aquino-Lemos et al., 2012). Lefferts et al. (2016) reported maintained accuracy but slower reaction times following a constant bout of matched-intensity cycling (55% $VO2_{MAX}$) in hypoxia ($FiO_2$ = 12.5%) compared to normoxia during an *n*-back task. It is likely that no differences in cognitive function following $HYP_{self-selected}$ were found as this assessment was carried out in normoxia following all experimental trials, whereby, $SpO_2$ was fully re-saturated (i.e., ≥96%). When the hypoxic stimulus is removed during interval walking for the same workload (i.e., during $NOR_{imposed}$), participants are less accurate in response to non-targets during the *n*-back task than $NOR_{self-selected}$. Elsewhere it has been shown that continuous moderate-, fixed-intensity treadmill exercise (60 mins at 65% $VO_{2PEAK}$, three times per week for 12 months) in normoxia decreases the obesity-dependent declines in cognitive function (Napoli et al., 2014). One explanation for why cognitive function was negatively impacted following $NOR_{imposed}$ may relate to the absence of hypoxic-induced physiological stress (i.e., lower HR, higher $SpO_2$ compared to $HYP_{self-selected}$) following a single session of interval walking at a matched intensity (i.e., velocity), as highlighted previously (Lambourne et al., 2010). Overall, perceptually-regulated interval walking in hypoxia and normoxia does not impact cognitive function of obese individuals, but negative effects are found in the absence of hypoxia at a matched velocity.

### *6.6.3. Limitations and perspectives*

The present study has several limitations, similar to that of study 1 (chapter 4). Firstly, conclusions are based on the recruitment of overweight and stage I obese individuals, which may underestimate the responses in stage II and III obesity to interval walking in hypoxia. Secondly, a single hypoxic dose ($FiO_2$ = 13.0%) was implemented during hypoxic sessions based on current literature (Navarette-Opazo & Mitchell, 2014). It is unknown whether this $FiO_2$ is the threshold (i.e., inducing a sufficient physiological stress compared to normoxia without negatively impacting performance of interval walking) for obese individuals walking in hypoxia, or whether a lower $FiO_2$ permits performance aligned with greater expected physiological stress in this type of population. The findings of this study build on previous work (study 1, chapter 4) (Hobbins et al., 2019a), utilising shorter over longer interval walking cycles to maximise the psycho-physiological responses in obese individuals during hypoxic exposure. Further work should look to distinguish whether varying the hypoxic dose (i.e., severity and duration), interval exercise (i.e., duration) and intensity (i.e., perceptually-regulated target RPE) leads to more favourable acute psycho-physiological responses when carried out in hypoxia compared to normoxia.

## 6.7. Conclusion

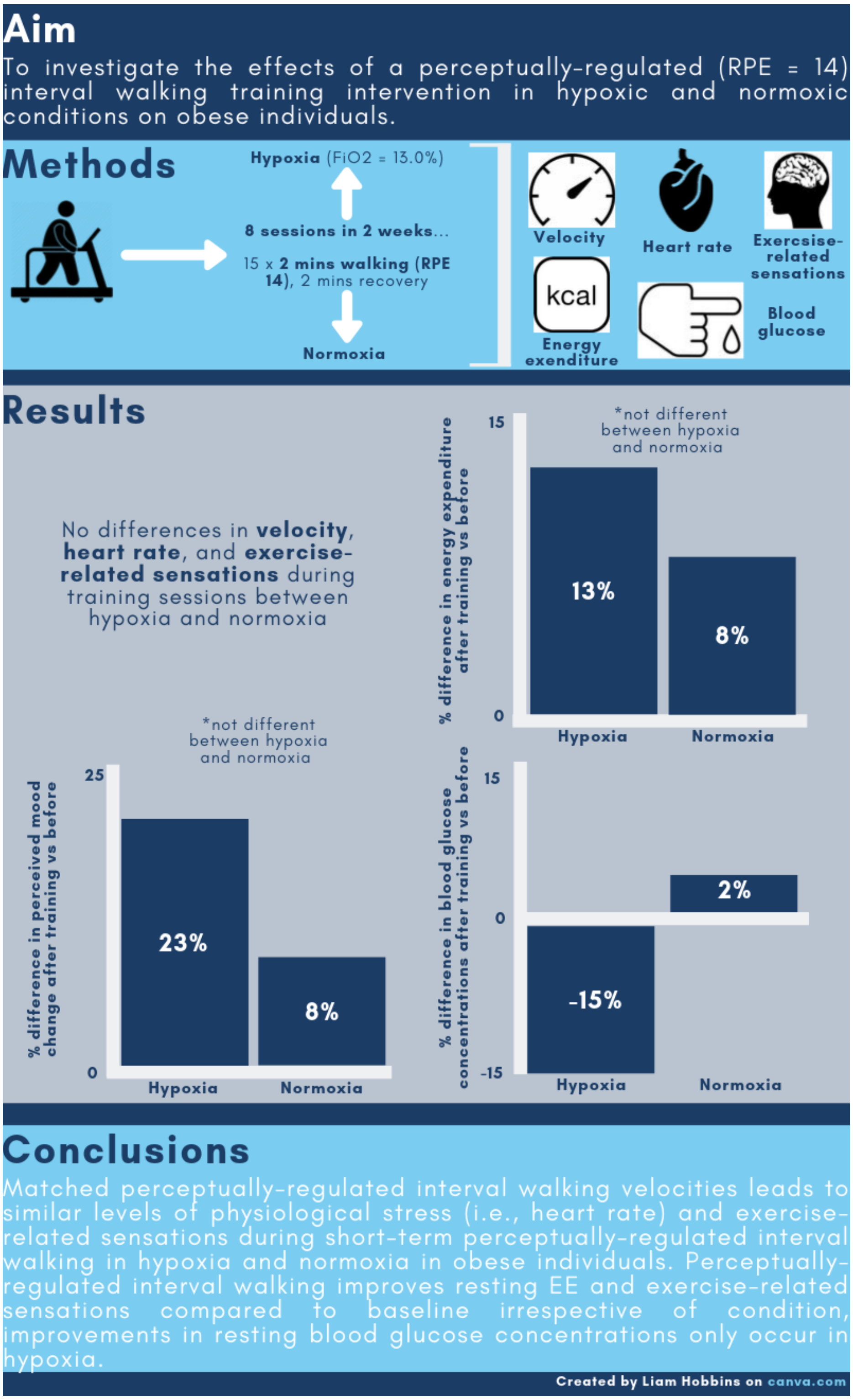
In conclusion, obese individuals can achieve a higher internal load (i.e., physiological stress) during perceptually-regulated interval walking in hypoxia at a progressively slower velocity compared to normoxia which is also perceived as less uncomfortable in their legs. Although exercise-related sensations are negative impacted after perceptually-regulated interval walking in hypoxia compared to normoxia (i.e., perceived mood change and exercise self-efficacy), these findings add to the acute, therapeutic benefits of hypoxic training for obese individuals. Also, these benefits are due to the effects of hypoxia *per se*, rather the adjusted velocity required to match an RPE target of 14.

## 6.8. Importance of findings for subsequent chapter and thesis

The findings of the current study partially support the data presented in the previous chapter (study 2, chapter 4), in the sense that utilising the perceptually-regulated exercise model in hypoxic conditions may provide viable options for obese individuals to carry out regular exercise for better psycho-physiological stimulation than normoxia. The acute effects are generally positive (i.e., a lower velocity achieves larger physiological stress for lower perceived limb discomfort in hypoxia *versus* normoxia). However, short-term perceptually-regulated interval walking for as little as two weeks (Morishima et al., 2015) may potentiate further positive psycho-physiological responses, and possible weight loss, in obese individuals. Therefore, the following study will address this.

# 7. Psycho-physiological responses to short term, perceptually-regulated interval walking training in hypoxia *versus* normoxia in obese individuals

## 7.1. Graphical abstract



**Aim**

To investigate the effects of a perceptually-regulated (RPE = 14) interval walking training intervention in hypoxic and normoxic conditions on obese individuals.

**Methods**

**8 sessions in 2 weeks...**

15 x **2 mins walking (RPE 14)**, 2 mins recovery

**Results**

No differences in **velocity**, **heart rate**, and **exercise-related sensations** during training sessions between hypoxia and normoxia

**Conclusions**

Matched perceptually-regulated interval walking velocities leads to similar levels of physiological stress (i.e., heart rate) and exercise-related sensations during short-term perceptually-regulated interval walking in hypoxia and normoxia in obese individuals. Perceptually-regulated interval walking improves resting EE and exercise-related sensations compared to baseline irrespective of condition, improvements in resting blood glucose concentrations only occur in hypoxia.

## 7.2. Abstract

**Aim** Whether a short-term, perceptually-regulated interval walking training intervention in hypoxia leads to more positive psycho-physiological responses during and after compared to normoxia.

**Methods** Sixteen obese adults (BMI = 33 ± 3 kg/m) completed eight perceptually-regulated (RPE = 14) interval walking sessions (15 × 2 mins walking/2-min resting) in two weeks. Half of the participants completed their sessions in hypoxia ($FiO_2 = 13.0\%$, HYP) and the other half in normoxia (NOR).

**Results** $SpO_2$ was lower throughout all HYP (83 ± 1%) training sessions compared to NOR (96 ± 1%, $p < 0.05$), whilst treadmill velocity, heart rate and exercise-related sensations remained similar across the training intervention. Lower resting blood glucose concentrations occurred only after HYP compared to baseline (-14.8 ± 1.2%, $p = 0.05$). Improvements in EE (+9.6 ± 2%, $p = 0.06$), perceived mood state (+11.8 ± 2.7%, $p = 0.06$) and exercise self-efficacy (+10.6 ± 4.1%, $p = 0.03$) were found after training *versus* baseline irrespective of condition.

**Conclusions** Short-term perceptually-regulated interval training in hypoxia could be implemented as an alternative strategy to current hypoxic conditioning recommendations as this leads to larger positive health improvements in obese individuals compared to normoxia despite matched training workloads.

## 7.3. Introduction

The previous experimental studies in the present thesis (chapters 4–6) have focused on the acute psycho-physiological responses to a single session of passive and active (perceptually-regulated intensity) normobaric hypoxic conditioning. It has been shown that short, frequent cycles of hypoxia interspersed with normoxia during a single passive hypoxic conditioning session are perceptually more tolerable, in relation to breathlessness, compared to longer, less frequent (study 1, chapter 4). A single session of active hypoxic conditioning (i.e., interval walking/running) leads to lower perceptually-regulated velocities yet providing similar or greater levels of physiological stress compared to normoxia (studies 2 and 3, chapters 5 and 6). Although exercise-related sensations are diminished in trained runners, obese individuals perceive perceptually-regulated interval walking in hypoxia as less strenuous on their lower limbs *versus* normoxia when utilising short, frequent cycles (based on study 1, chapter 4 findings). Taking into account these positive findings collectively, it could be argued that a short-term training period of perceptually-regulated interval walking in hypoxia may lead to further psycho-physiological benefits compared to acute, and in reference to normoxia.

Studies reporting the positive effects of exercising in hypoxia on health markers in obese individuals are unequivocal to date. Greater reductions in total body (Kong et al., 2013, Netzer et al., 2008) and fat mass (Wiesner et al., 2009) have been reported following training in hypoxic compared to normoxic conditions. Elsewhere, Gatterer et al. (2015) showed similar losses in body mass between training in hypoxia and normoxia, whilst improvements in blood pressure (Park & Lim, 2017), glucose concentrations (De Groote et al., 2018) and metabolic rate (Wiesner et al., 2009) have been found to occur to a greater extent following hypoxia *versus* normoxia. Further, matched improvements (Wiesner et al., 2009) and maintenance (Haufe et al., 2008) in functional fitness (i.e., $VO_{2MAX}$) following hypoxic and normoxic training have also been found. The common factor between these studies regards the training duration (4–6 weeks). Burgess et al. (2017) showed that early weight loss success (within 2–4 weeks of initiating an intervention) is a prominent predictor of exercise adherence. Therefore, it could be argued that shorter training interventions in hypoxia than those implemented within the current literature available may lead to further long-term psycho-physiological benefits. In support of this, it has been shown that a two-week training intervention in hypoxia (12 × 60 mins cycling at 65% relative $VO_{2MAX}$, $FiO_2 = 15.0\%$) leads to similar improvements in $VO_{2MAX}$ and mean blood pressure in obese individuals as the same amount of sessions spread over a four-week intervention. Therefore, identifying potential earlier positive metabolic responses, exercise-related sensations and cognitive function could improve the confidence and likelihood of obese individuals in adhering to regular exercise (i.e., exercise self-efficacy).

In addition to training duration, the aforementioned studies implement a fixed-intensity of exercise (60–70% $VO_{2MAX}$) (de Groote et al., 2018, Gatterer et al., 2015, Haufe et al., 2008, Kong et al., 2013, Netzer et al., 2008, Park & Lim, 2017, Wiesner et al., 2009). A perceptually-regulated exercise intensity may be more enjoyable than a fixed-intensity (Ekkekakis & Linds, 2006), potentially further increasing adherence. When exercising at a perceptually-regulated intensity, it has been demonstrated, in an obese population, that a progressively lower external workload (i.e., treadmill velocity) leads to a higher physiological stress (i.e., HR) and lower exercise-related sensations (i.e., perceived limb discomfort) during a single hypoxic *versus* normoxic interval walking (15 × 2/2 mins) session (study 3, chapter 6). In addition, greater enjoyment (Kong et al., 2016a) and lower exertion (Kong et al., 2016b) result from interval *versus* continuous training irrespective of hypoxia in the same demographic of participants. No study has investigated the simultaneous physiological and psychological responses to short-term perceptually-regulated interval walking in hypoxic *versus* normoxic conditions in obese individuals. Taking into account the current literature, this novel type of training intervention may mitigate the negative implications of initiating and maintaining an exercise intervention for obese individuals by inducing significant physiological stress for positive effects, maintaining exercise-related sensations and leading to long-term adherence when in hypoxia compared to normoxia all whilst under control of the individual exercising. Therefore, the aim of the current study was to investigate the effects of a perceptually-regulated (RPE = 14) interval walking training intervention in hypoxic and normoxic conditions on obese individuals. It was hypothesised that the self-paced treadmill velocity will be slower throughout training carried out in hypoxic compared to normoxic conditions, but improvements in physiological and metabolic responses, and exercise-related sensations would be similar and cognitive function maintained between conditions after training compared to before.

## 7.4. Methods

### *7.4.1. Participants*

After meeting the eligibility criteria and providing written informed consent, sixteen obese (Table 7.3. for anthropometric data) individuals participated in this study. This study received ethical approval from the School of Applied Sciences Ethics Committee, LSBU (SAS1822).

### *7.4.2. Experimental design*

Participants completed eleven separate visits across three consecutive weeks. The first session (visit 1) consisted of eligibility determination, familiarisation with the measures and treadmill walking, and identification of the walking velocity associated with an RPE = 14. Within 72 h, participants returned to the lab for pre-training measurements (visit 2), which consisted of assessment of anthropometrics (body mass and height), physiological (blood pressure) and metabolic (EE, substrate utilisation and glucose concentrations) measures, exercise-related sensations (perceived mood change and exercise self-efficacy) and functional fitness. After 24–72 h, participants undertook the first of eight supervised 60-min self-paced interval walking sessions (visits 3–10) which were completed within a two week period. This present study compared two separate groups of different obese individuals, whereby, half of the participants completed their sessions in hypoxic conditions ($FiO_2$ = 13.0%, equivalent to ~3500 m elevation above sea level; HYP), and the other half completed their sessions in normoxic conditions (sea level, NOR). Training conditions were randomly allocated. The format of the interval walking sessions were identical to the perceptually-regulated sessions in study 3 (chapter 6) as described previously (3.7.). Velocity, HR and $SpO_2$ were measured during interval walking, whilst perceived recovery and motivation, and perceived breathlessness, limb discomfort were measured before and after, respectively, each session. Before and after the first and last interval session, cognitive function (accuracy and reaction time were measured. Within 72 h of the final perceptually-regulated interval walking session, participants returned to the lab (visit 11) for re-assessment of anthropometrics, physiological and metabolic responses, exercise-related sensations and functional fitness.

### *7.4.3 Familiarisation session*

Participants were firstly familiarised with the perceptual scales, cognitive test and walking on the treadmill (Pulsar, h/p/cosmos, Germany). Secondly, preferred walking velocity was determined (3.7.). After 10 mins of rest, participants completed one 2-min interval composing the interval walking protocol (see below) for habituation. After 5 mins of rest, participants completed a 6-min bout of perceptually-regulated continuous walking for familiarity with assessment of functional fitness (3.13.).

### *7.4.4. Pre- and post-training measurements session*

Participants arrived at the lab following an 8 h fasting period (water exempt). Height and weight were assessed. After 10 mins of rest to enable stabilisation of haemodynamics, participants were attached with a facemask to collect a 5-min sample of expired gas. Blood pressure, as well as exercise-related sensations were assessed, and a capillary blood sample for resting glucose concentrations was drawn. Participants completed a standardised warm up (5 mins at 3 km/h) before 6 mins of perceptually-regulated continuous walking in normoxic conditions for determination of functional fitness. Participants were randomly allocated to a training condition after the pre-training measurements session.

### *7.4.5. Interval walking training intervention*

Participants completed eight supervised 60-min (15 × 2 mins walking at RPE = 14, 2 mins resting) perceptually-regulated interval walking sessions across two consecutive weeks in a commercial gym (Academy of Sport, London South Bank University). Each session began with a 5-min warm up at 3.0 km/h on the treadmill (Fusion Run Series3, Pulse Fitness, UK). A facemask connected to a portable hypoxic generator (3.8.) was then attached to the participants. During all sessions, the first 30 s of each 2-min interval began at participants' perceptually-regulated walking velocity (RPE = 14). Following this, participants were able, every 30 s, to decide if and how treadmill velocity needed to be altered (i.e., self-paced and adjusted manually by the investigator) to ensure maintenance of an RPE of 14 whilst walking (3.7.).

### *7.4.6. Hypoxic conditioning*

Participants wore a facemask (Altitude Training Mask, Hypoxico Altitude Training Systems, USA) connected *via* corrugated plastic tubing to a hypoxic generator (Everest Training Summit II, Hypoxico Altitude Training Systems, USA) to create hypoxic conditions (3.8.). The $FiO_2$ provided in this study was 13.0% (simulated altitude of ~3500 m), deemed safe in the population studied (Navarrete-Opazo & Mitchell, 2014). As used in the previous studies of the current thesis, the blinding procedure for those in NOR included the hypoxic generator being switched on and set at a simulated altitude of ~100 m (3.8.). Total hypoxic exposure corresponded to exactly 480 mins with the facemask remaining attached during all training sessions for those in the HYP group.

### *7.4.7. Measures*

#### *7.4.7.2. During training*

Treadmill velocity, HR (3.9.1.) and $SpO_2$ (3.9.2.) were manually recorded every 30 s during each 2-min interval.

Perceived recovery (3.11.1.) and motivation to exercise (3.11.2.) were assessed prior to the warm up of each session. Immediately after each session, ratings of perceived breathlessness (3.11.3.), limb discomfort (3.11.4.) and pleasure (3.11.5.) were assessed.

Cognitive function was assessed before (pre-exercise) and after (post-exercise) the first and last session *via* the *n*-back task (3.12.2.).

#### *7.4.7.2. Pre- and post-training measurements session*

Total body mass and height were assessed, which permitted calculation of BMI (3.2.2.).

Expired gas samples were collected during rest (5 mins) for assessment of EE and fuel utilisation in normoxic conditions (3.10.1.). The first and last 30 s of each 5-min sample were removed to nullify any fluctuations with measurement initiation/cessation and anticipation of mask removal and averaged for the subsequent 4 mins (Workman & Basset, 2012).

Blood pressure (3.9.3.), glucose concentrations (3.10.2.), perceived mood change (3.11.6.) and exercise self-efficacy (3.11.8.) were assessed at rest.

Functional fitness (3.13.) was assessed to complete the measurements session before and after training.

### *7.4.8. Data analysis*

Data were processed offline into Excel (Microsoft Office, 2016). Preliminary analysis (paired-sample, equal variance *t*-test) was carried out to determine whether pre-training (baseline) measurements were statistically significantly different between HYP and NOR. If statistical differences were found, data collected during and post-training were normalized to the pre-training measurement. Velocity, HR and $SpO_2$ were averaged across each 60-min session. Velocity, HR and exercise-related sensations recorded during sessions 2–8 were calculated as a percentage change from session 1 (100%) due to differences in the initial velocity deemed equal to RPE 14 between HYP and NOR. Target and non-target accuracy and reaction time were averaged across the cognitive task duration.

### *7.4.9. Statistical analysis*

A *t*-test was used to determine any statistically significant differences in the raw values of velocity, HR, $SpO_2$, and perceived recovery, motivation, breathlessness, limb discomfort and pleasure during session 1 (averaged across the session). A two-way repeated-measures mixed-design ANOVA was used to investigate the main effect of condition (HYP *versus* NOR), time (pre-training *versus* post-training or session 1 *versus* 2, 3, 4, 5, 6, 7 and 8) and the condition × time interaction.

## 7.5. Results

### *7.5.1. During training*

#### *7.5.1.1. Velocity*

Velocity was unaffected between conditions and over time ($p > 0.05$, Figure 7.1.A, Table 7.1.).

#### *7.5.1.2. HR & $SpO_2$*

HR was higher during the first session of HYP *versus* NOR (+10 ± 3%, Table 7.1.), but was unaffected between conditions and over time thereafter ($p > 0.05$, Figure 7.1.B). $SpO_2$ was lower during HYP *versus* NOR (83 ± 1% *versus* 96 ± 1%, respectively, $p < 0.05$), irrespective of time ($p > 0.05$, Figure 7.1.C, Table 7.1.).

### *7.5.1.3. Exercise-related sensations*

Perceived recovery was lower prior to session 4 (76 ± 16%, $p < 0.01$) and 7 (75 ± 19%, $p < 0.01$, Figure 7.2.A) compared to session 1, irrespective of condition. Perceived motivation was initially lower following the first session of HYP *versus* NOR (-19 ± 6%, $p = 0.01$, Table 7.1.), and then lower prior to session 2 (75 ± 12%), 3 (69 ± 20%), 4 (69 ± 14%), 5 (77 ± 16%), 7 (73 ± 17%) and 8 (71 ± 20%, $p < 0.04$, Figure 7.2.B) compared to session 1. Perceived breathlessness and limb discomfort were unaffected by condition and over time ($p > 0.05$, Figure 7.2.C–D, Table 7.1.). Perceived pleasure tended to be lower after HYP session 1 compared to NOR (-15 ± 4%, $p = 0.07$, Table 7.1.), with no difference between conditions and over time thereafter (Figure 7.2.E).

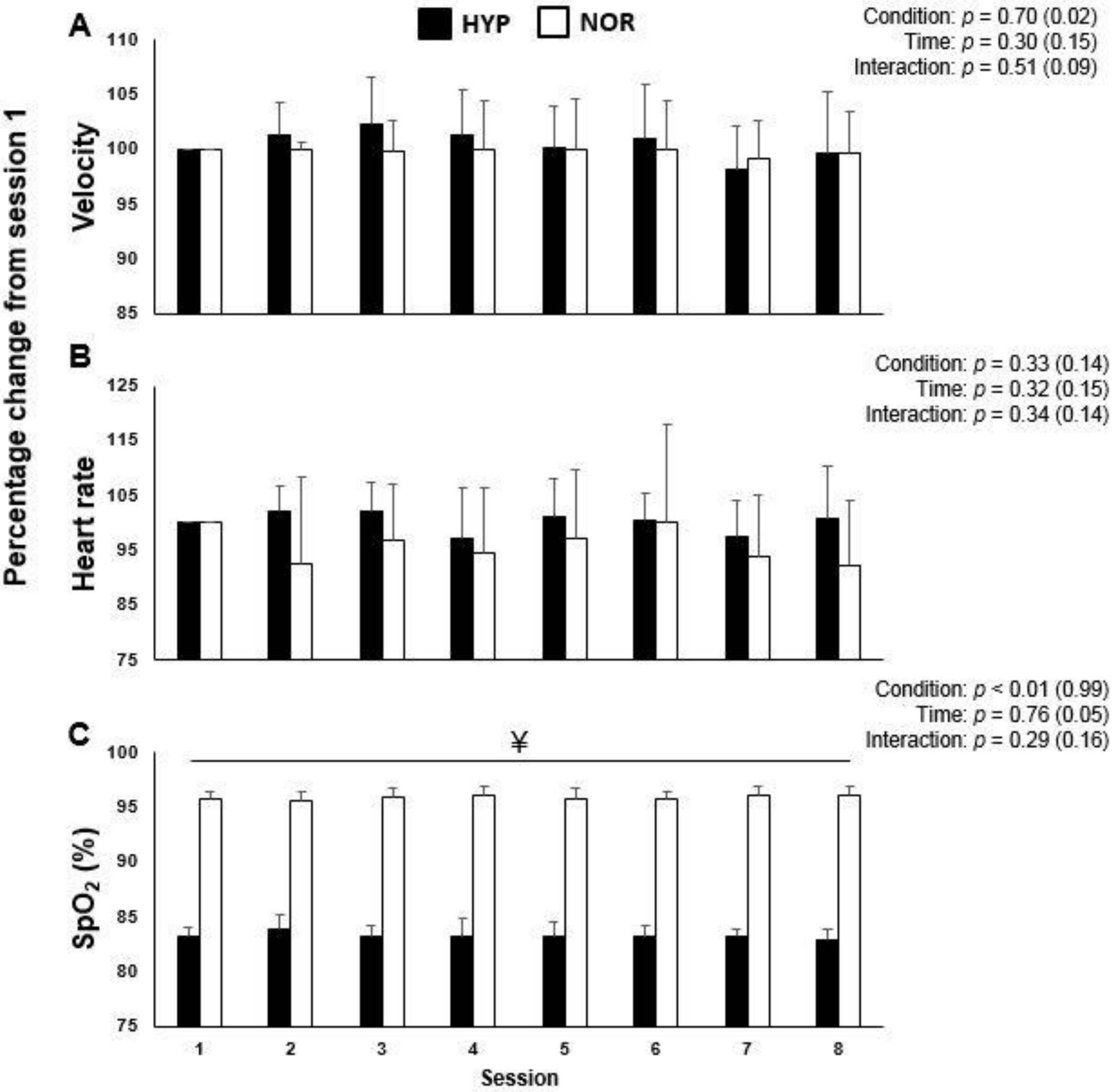


**Figure 7.1.** Changes in velocity (A) heart rate (B) and arterial oxygen saturation ($SpO_2$; C) during the interval walking training sessions. Data were recorded every 30 s during 2-min intervals, then averaged over the 60-min sessions. Velocity and heart rate from sessions 2–8 are calculated as a percentage difference from session 1 (100%). All data are presented as mean ± SD. ANOVA main effects of time, condition and interaction are stated along with partial-eta squared for effect size into brackets. Black bars = interval walking in hypoxia (HYP); white bars = interval walking in normoxia (NOR). ¥ denotes a statistically significant difference ($p < 0.05$) between HYP *versus* NOR .

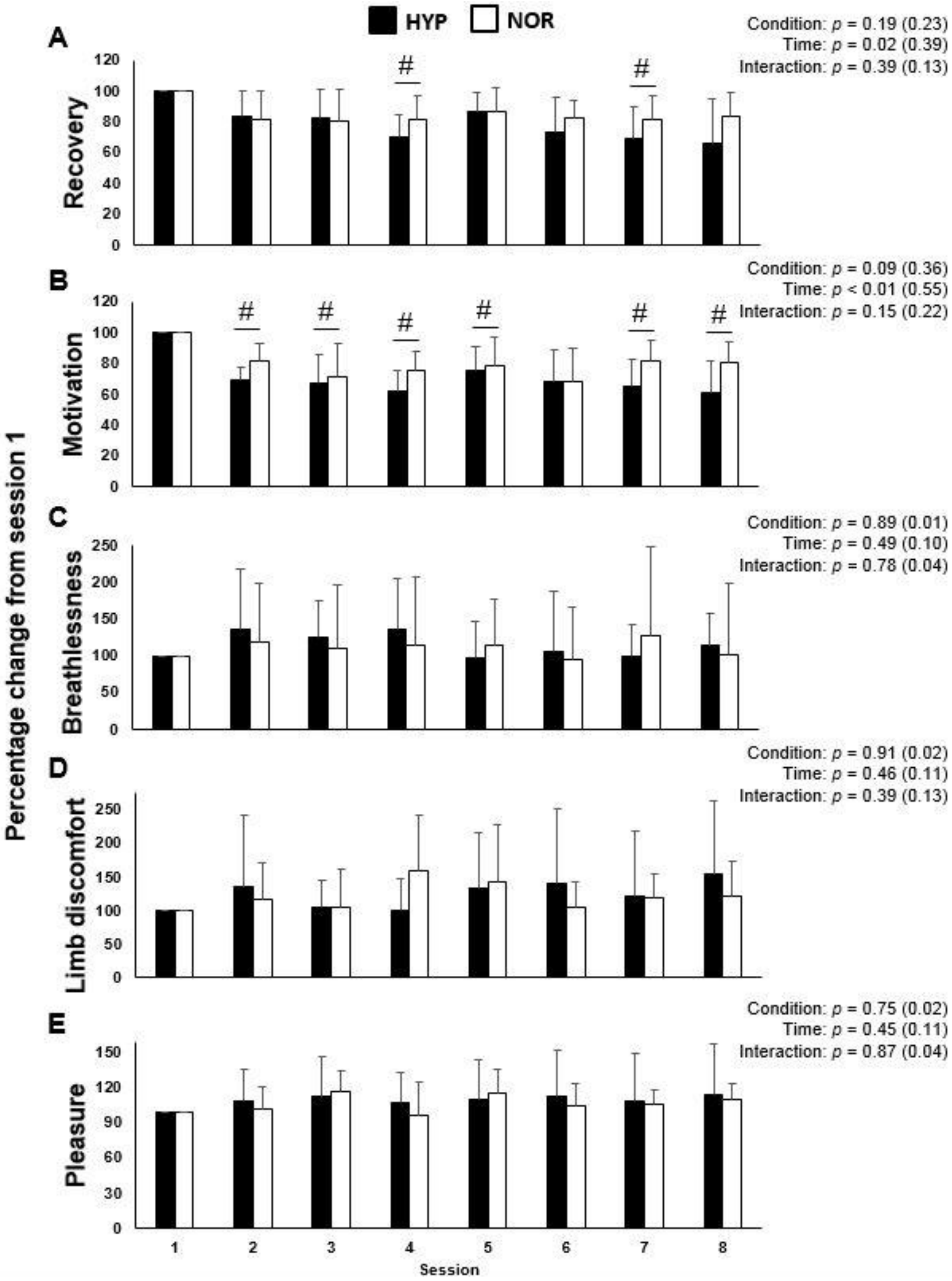


**Figure 7.2.** Changes in perceived recovery (A) and motivation (B) and breathlessness (C), limb discomfort (D) and pleasure (E) assessed before and after the interval walking training sessions, respectively. Data from sessions 2–8 are calculated as a percentage difference from session 1 (100%) and presented as mean ± SD. ANOVA main effects of time, condition and interaction are stated along with partial-eta squared for effect size into brackets. Black bars = interval walking in hypoxia (HYP); white bars = interval walking in normoxia (NOR). # denotes a statistically significant difference ($p < 0.05$) for a given session *versus* session 1.

#### *7.5.1.4. Cognitive function*

Compared to pre-training, non-target accuracy improved post-training at pre-exercise (73 ± 26% *versus* 82 ± 25%, $p < 0.05$, Table 7.2.), irrespective of condition ($p > 0.05$). All other cognitive function parameters were unaffected between conditions and over time ($p > 0.05$, Table 7.2.).

### *7.5.2. Pre- versus post-training*

#### *7.5.2.1. Anthropometrics*

Body mass and BMI were unaffected between conditions and over time ($p > 0.05$, Table 7.3.).

#### *7.5.2.2. Functional fitness*

Functional fitness was unaffected between conditions and over time ($p > 0.05$, Table 7.3.).

#### *7.5.2.3. Metabolism*

Resting glucose concentrations were lower in HYP than NOR post-training (-14.8 ± 1.2% *versus* +2.3 ± 1.1%, respectively, $p = 0.05$, Figure 7.3.). Compared to pre-training, resting EE tended to be higher post-training (+9.6 ± 2%, $p = 0.06$, Table 7.3.) irrespective of condition ($p > 0.05$). Resting fat and glucose metabolism were unaffected between conditions and over time ($p > 0.05$, Table 7.3.).

#### *7.5.2.4. Blood pressure*

Systolic and diastolic blood pressure were unaffected between conditions and over time ($p > 0.05$, Table 7.3.).

#### *7.5.2.5. Exercise-related sensations*

Compared to pre-training, post-training perceived mood state (3.8 ± 1.7 *versus* 3.4 ± 1.7 au, $p = 0.06$, Figure 7.4.A) and exercise self-efficacy (73 ± 32% *versus* 66 ± 27%, $p = 0.03$, Figure 7.4.B) improved, irrespective of condition ($p > 0.05$).

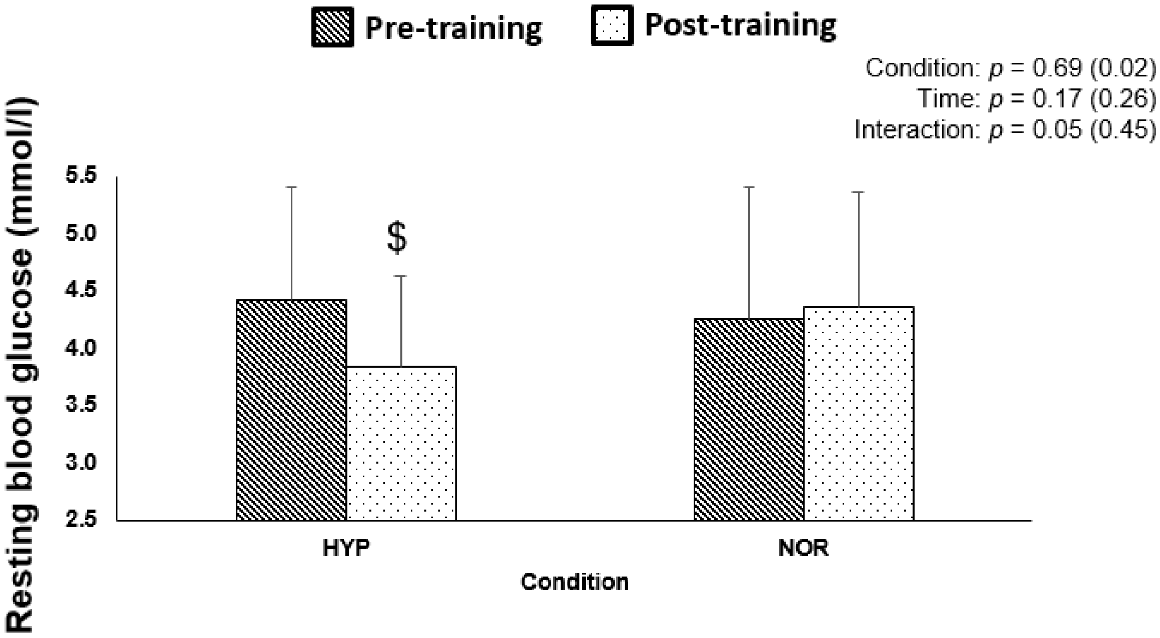


**Figure 7.3.** Changes in resting blood glucose levels measured pre- and post-training. Data are presented as mean ± SD. ANOVA main effects of time, condition and interaction are stated along with partial-eta squared for effect size into brackets. Black lined bars = pre-training; black dotted bars = post-training. $ denotes a statistically significant difference ($p < 0.05$) *versus* post-training in normoxia.

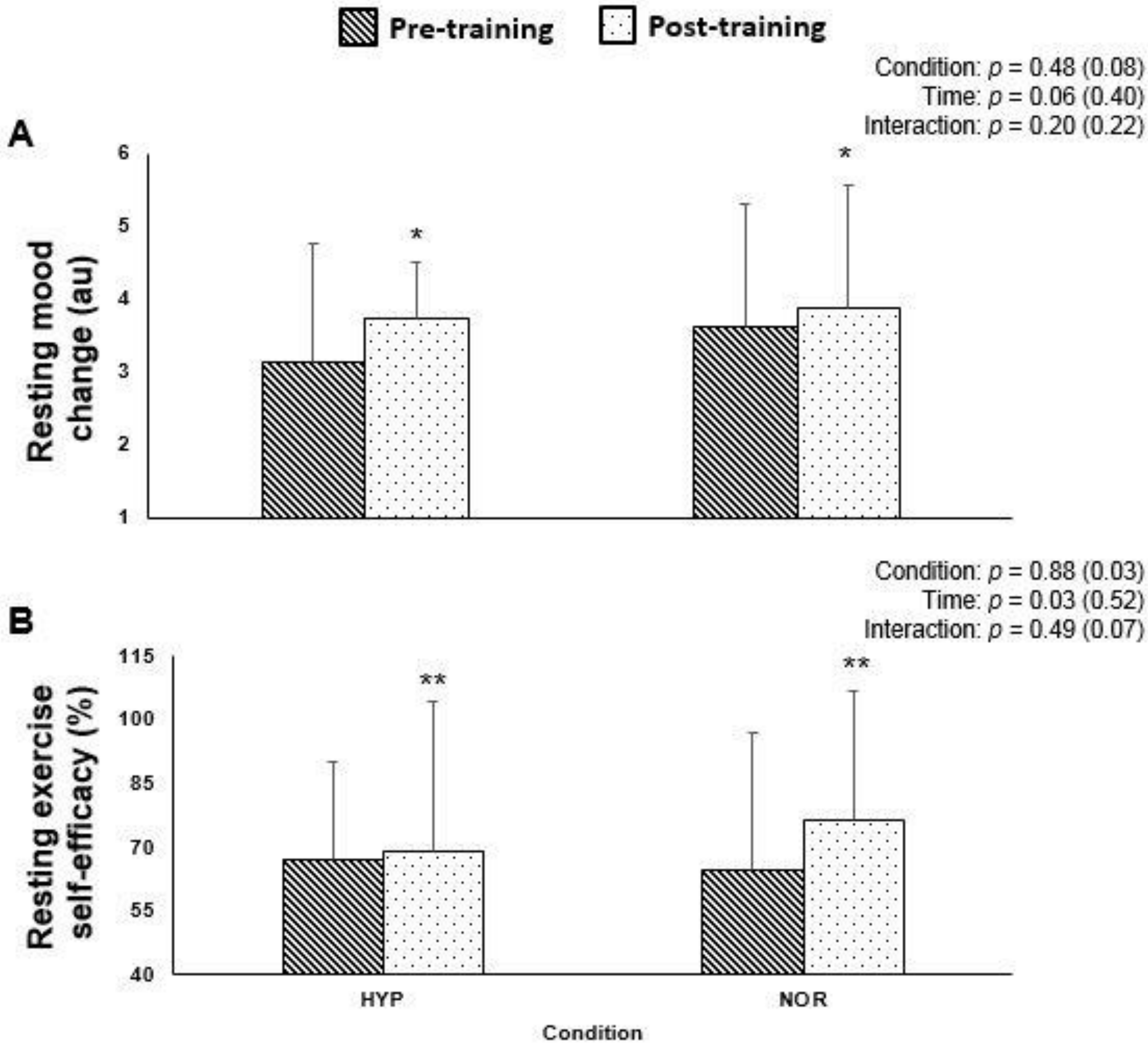


**Figure 7.4.** Changes in perceived resting mood change (A) and exercise self-efficacy (B) measured pre- and post-training. Data are presented mean ± SD. ANOVA main effects of time, condition and interaction are stated along with partial-eta squared for effect size into brackets. Black lined bars = pre-training; black dotted bars = post-training. ** and * denotes a statistically significant difference ($p < 0.05$) and a trend for significance ($p < 0.06$), respectively, *versus* pre-training.

**Table 7.1.** Velocity, HR, $SpO_2$ and perceived recovery, motivation, breathlessness, limb discomfort and pleasure during session 1 (averaged across the session).

| | Condition | | |
|---|---|---|---|
| **Parameter** | **HYP** | **NOR** | ***t*-test *p* value** |
| Velocity (km/h) | 6.5 ± 0.3 | 6.3 ± 0.6 | 0.23 |
| HR (bpm) | 144 ± 16 | 129 ± 20 | 0.04 |
| $SpO_2$ (%) | 83.2 ± 0.9$^{\#\#}$ | 95.7 ± 0.7 | 0.01 |
| Perceived recovery (au) | 8.4 ± 1.6 | 8.1 ± 1.9 | 0.38 |
| Perceived motivation (au) | 13.8 ± 1.8$^{\#\#}$ | 16.4 ± 2.3 | 0.01 |
| Perceived breathlessness (au) | 2.5 ± 1.3 | 2.3 ± 1.4 | 0.28 |
| Perceived limb discomfort (au) | 3.3 ± 2.1 | 2.4 ± 1.7 | 0.15 |
| Perceived pleasure (au) | 12.4 ± 1.5$^{\#}$ | 14.3 ± 3.5 | 0.07 |

Data presented as mean ± SD. HR = heart rate, HYP = hypoxic condition, NOR = normoxic condition, $SpO_2$ = arterial oxygen saturation. $^{\#\#}$ denotes a statistically significant difference ($p \leq 0.05$) *versus* NOR, $^{\#}$ denotes a statistically significant trend ($p \leq 0.07$) *versus* NOR.

**Table 7.2.** Cognitive function data measured before (pre-exercise) and after (post-exercise) sessions 1 and 8.

| | | **HYP** | | **NOR** | | **ANOVA *p* value (effect size)** | | |
|---|---|---|---|---|---|---|---|---|
| **Parameter** | **Time point** | **Session 1** | **Session 8** | **Session 1** | **Session 8** | **Condition** | **Time** | **Interaction** |
| Target accuracy (%) | Pre-exercise | 64 ± 29 | 78 ± 16 | 83 ± 12 | 76 ± 31 | 0.18 (0.25) | 0.46 (0.08) | 0.44 (0.09) |
| | Post-exercise | 70 ± 24 | 78 ± 23 | 83 ± 22 | 81 ± 11 | 0.42 (0.09) | 0.50 (0.06) | 0.40 (0.10) |
| Target reaction time (ms) | Pre-exercise | 475 ± 109 | 479 ± 119 | 575 ± 212 | 651 ± 331 | 0.26 (0.17) | 0.09 (0.35) | 0.45 (0.08) |
| | Post-exercise | 486 ± 134 | 443 ± 156 | 579 ± 263 | 586 ± 316 | 0.37 (0.11) | 0.63 (0.04) | 0.50 (0.07) |
| Non-target accuracy (%) | Pre-exercise | 65 ± 29 | 86 ± 15** | 82 ± 20 | 78 ± 32** | 0.63 (0.03) | 0.05 (0.46) | 0.18 (0.24) |
| | Post-exercise | 86 ± 14 | 89 ± 11 | 90 ± 14 | 91 ± 16 | 0.69 (0.02) | 0.38 (0.11) | 0.39 (0.11) |
| Non-target reaction time (ms) | Pre-exercise | 445 ± 135 | 509 ± 112 | 523 ± 118 | 567 ± 238 | 0.37 (0.12) | 0.13 (0.30) | 0.85 (0.01) |
| | Post-exercise | 538 ± 174 | 509 ± 119 | 553 ± 172 | 541 ± 220 | 0.81 (0.01) | 0.43 (0.09) | 0.69 (0.03) |

Data presented as mean ± SD. HYP = hypoxic condition, NOR = normoxic condition. ** denotes a statistically significant difference ($p < 0.05$) *versus* pre-training.

**Table 7.3.** Anthropometric, metabolism, blood pressure and functional fitness data measured pre- and post-training.

| | | **HYP** | | **NOR** | | **ANOVA *p* value (effect size)** | | |
|---|---|---|---|---|---|---|---|---|
| | **Parameter** | **Pre** | **Post** | **Pre** | **Post** | **Condition** | **Time** | **Interaction** |
| | Gender | 4 M, 4 F | | 5 M, 3 F | | | | |
| | Age (years) | 32.1 ± 10.2 | | 41.1 ± 13.0 | | N/a | N/a | N/a |
| | Height (m) | 1.7 ± 0.9 | | 1.7 ± 0.1 | | | | |
| | Total body mass (kg) | 92.2 ± 12.0 | 91.7 ± 11.9 | 95.5 ± 9.5 | 95.5 ± 10.0 | 0.55 (0.05) | 0.45 (0.08) | 0.56 (0.05) |
| | BMI (kg/m) | 32.9 ± 3.6 | 32.6 ± 3.6 | 32.5 ± 1.4 | 32.0 ± 2,0 | 0.75 (0.02) | 0.21 (0.21) | 0.72 (0.02) |
| | EE (kcal/min) | 1.64 ± 0.33 | 1.86 ± 0.42* | 1.83 ± 0.36 | 1.98 ± 0.41* | 0.40 (0.10) | 0.06 (0.40) | 0.61 (0.04) |
| | Fat oxidation (kcal/min) | 1.10 ± 0.33 | 1.31 ± 0.42 | 1.23 ± 0.39 | 1.39 ± 0.58 | 0.49 (0.07) | 0.16 (0.27) | 0.75 (0.02) |
| | Glucose oxidation (kcal/min) | 0.47 ± 0.16 | 0.48 ± 0.36 | 0.52 ± 0.29 | 0.51 ± 0.32 | 0.59 (0.04) | 0.99 (0.01) | 0.91 (0.01) |
| Blood pressure | Systolic | 119 ± 8 | 117 ± 14 | 132 ± 14 | 125 ± 17 | 0.19 (0.23) | 0.22 (0.20) | 0.40 (0.10) |
| (mmHg) | Diastolic | 77 ± 9 | 74 ± 6 | 84 ± 8 | 81 ± 7 | 0.07 (0.39) | 0.10 (0.34) | 0.88 (0.01) |
| | Functional fitness (m) | 669.9 ± 43.4 | 680.3 ± 72.0 | 612.9 ± 87.6 | 618.3 ± 101.7 | 0.11 (0.31) | 0.58 (0.05) | 0.74 (0.02) |

Data presented as mean ± SD. BMI = body mass index, EE = energy expenditure, F = females, HYP = hypoxic condition, M = males, NOR = normoxic condition. * denotes a statistically significant trend ($p \leq 0.06$) *versus* pre-training.

## 7.6. Discussion

The aim of the current study was to investigate whether a short-term (perceptually-regulated RPE = 14) interval walking training intervention leads to similar improvements in body mass, physiological and metabolic responses, and exercise-related sensations whilst maintaining cognitive function for a lower external workload in hypoxic *versus* normoxic conditions in obese individuals. The main findings show matched external (i.e., treadmill velocity) and internal (i.e., HR) workloads between hypoxic and normoxic conditions, whilst perceived recovery and motivation was reduced across the training intervention irrespective of condition. Perceptually-regulated interval walking in hypoxia reduced resting blood glucose levels after training compared to before, whilst resting EE (trend) and exercise-related sensations improved irrespective of condition. No changes were found in body mass and cognitive function between conditions following the training intervention. Overall, the addition of hypoxia to a short-term perceptually-regulated exercise training model maintained psycho-physiological responses during the training period. Time-dependent increases in metabolic responses and exercise-related sensations highlight the positive benefits of perceptually-regulated interval walking in obese individuals, whilst improvements in obesity-associated health markers (i.e., resting glucose concentrations) arise only with the inclusion of hypoxia.

### *7.6.1. Measures assessed during training*

The perceptually-regulated intensity (i.e., self-selected velocity) during walking did not differ between training conditions, nor over time. Furthermore, the physiological stress (i.e., HR) recorded during interval walking was unaffected by hypoxia and across sessions (after session 1). This is somewhat different to findings reported in the literature, whereby, a lower workload (-7–28%) was implemented during training (30–60 mins cycling/running/walking continuously at a fixed, moderate intensity, thrice weekly, 3–4 weeks) in hypoxia ($FiO_2$ =

~15.0%) compared to normoxia, which lead to similar levels of physiological stress (i.e., matched HR) (Haufe et al., 2008, Pramsohler et al., 2017, Wiesner et al., 2010). The findings of the present study likely differ from the aforementioned due to implementation of interval walking (2 mins walking, 2 mins resting), subsequently permitting a maintenance in total workload following short, interspersed recovery periods compared with moderate-intensity, continuous exercise (Gibala et al., 2014). In essence, the 2-min recovery periods implemented in the current study based on the findings of study 1 (chapter 4) and 3 (chapter 6) of the present thesis may have permitted sufficient recovery in HR. However, the previous two studies in this thesis (2 and 3, chapters 5 and 6) concluded that lower workloads are self-selected to maintain a target RPE more so when carrying out a single interval running/walking session in hypoxia compared to normoxia. Lower workloads in hypoxia *versus* normoxia may not have occurred in the current study due to maintenance of the RPE target across the intervention. Fernendez-Menendez et al. (2018) showed that preferred walking speed (RPE ~10) became progressively faster over a 3 week intervention in both hypoxic and normoxic conditions but remained slower in hypoxia compared to normoxia. If the RPE target in the current study was increased during week 2 compared to week 1, it is possible that a slower walking velocity would have been selected in hypoxia compared to normoxia to match the RPE target. In summary, a matched perceptually-regulated intensity during a two-week period of interval walking in hypoxic and normoxic conditions leads to similar treadmill velocities and HR levels in obese individuals.

As the perceptually-regulated interval walking intensity was matched between conditions, it may have been expected that exercise-related sensations would have been negatively impacted in HYP compared to NOR due to the potent stress of hypoxia challenging RPE during exercise (Koglin & Kayser, 2013). Unlike studies 2 and 3 (chapters 5 and 6), this was not the case in the current study. Jefferies et al. (2019) reported decreased $SpO_2$ (~14%) as an explanation for a shorter time to exhaustion during a cycling task (clamped at RPE 16) in hypoxia ($FiO_2$ =

11.4%) than normoxia. Even though $SpO_2$ decreases in the current study are similar to Jefferies et al. (2019), the hypoxic stimulus was less severe ($FiO_2$ = 13.0%). Therefore, it could be implied that a more severe $FiO_2$ negatively impacts exercise-related sensations during perceptually-regulated exercise, as shown elsewhere (Girard et al., 2017). Importantly, the present study found time-dependent decreases in perceived recovery and motivation irrespective of environmental condition. As described by Ekkekakis & Lind (2006), exercise-related sensations are important for adherence to regular exercise training. Future investigations should look to identify whether manipulating the perceptually-regulated intensity (RPE target) and duration (work/rest ratio) in hypoxic conditions will accommodate more positive exercise-related sensations in obese individuals. Collectively, exercise-related sensations are maintained during perceptually-regulated interval walking in hypoxic and normoxic conditions, despite time-dependent decreases in perceived recovery and motivation. Cognitive function was unaffected by short-term, perceptually-regulated interval training (walking) in hypoxia and normoxia. This can be considered a positive finding given that decreases in cognitive function are often associated with increases in BMI (Smith et al., 2011). Schega et al. (2016) showed that Stroop test performance improved following a combination of normoxic exercise (30 mins submaximal, fixed-intensity, three sessions per week for four weeks) and passive hypoxic conditioning (90 mins $SpO_2$ clamp = 90–80%) *versus* normoxic exercise and exposure. Cognitive function may have not differed between conditions in the present study due to assessment being carried out in normoxia, the relatively short training period, or participants may have acclimated to the demands of hypoxia within the training period compared with normoxia. Although no greater improvements in cognitive function were found following HYP compared to NOR, better resting non-target accuracy was found prior to session 8 than session 1. This improvement is a positive outcome for obese individuals, and implies that after perceptually-regulated interval walking, obese individuals are able to more accurately identify un-associated items during a cognitive function task than before training. Overall, short-term, perceptually-regulated interval walking has limited (if any) impact on cognitive function, irrespective of hypoxic and normoxic conditions, in obese individuals.

### *7.6.2. Measures assessed pre- versus post-training*

Total body mass, BMI and functional fitness were not different after training compared to before in both HYP and NOR. Within the literature, larger (Kong et al., 2013, Netzer et al., 2008) and similar improvements (Gatterer et al., 2015) of body composition have been found following hypoxic *versus* normoxic training. Similarly, improvements in functional fitness have been reported after hypoxic *versus* normoxic training (Haufe et al., 2008, Wiesner et al., 2009). In the current study, a two-week training period was implemented as a practical and time-efficient (i.e., total training period duration) strategy. Morishima et al. (2015) showed that a two-week intervention (60 mins cycling at 65% relative $VO_{2MAX}$, $FiO_2$ = 15.0%, six times per week) led to similar improvements in $VO_{2MAX}$ and mean blood pressure of sedentary males as a four-week intervention with the same total amount of sessions. It may have been that for obese individuals, the duration of a two week training block is not long enough to elicit positive changes in body composition and functional fitness, unlike studies implementing longer training periods (4–6 weeks) with a similar number of training sessions (8–12) (Haufe et al., 2008, Kong et al., 2014, Netzer et al., 2008). The current dataset shows that blood pressure is not different to baseline following perceptually-regulated interval walking in HYP and NOR. Even though the obese individuals who participated in the current study were normotensive, it has been established that the additive stress of exercising in hypoxia on the autonomic nervous system at fixed intensities may induce further negative implications (Fletcher, 2001). Therefore, perceptually-regulated interval walking in hypoxia may be a safer option than fixed-intensity exercise in relation to exercise prescription to minimise cardiovascular stress. Overall, body mass, BMI, blood pressure and functional fitness is maintained following perceptually-regulated interval walking in hypoxic and normoxic conditions.

Following training, larger improvements in resting glucose concentrations were found after HYP compared to baseline. This finding is similar to the work of De Groote et al. (2018), showing improved glucose tolerance following hypoxic ($FiO_2$ = 15.0%) compared to normoxic training (50–60 mins endurance and resistance exercise, 3 times per week, 6 weeks) in obese adolescents. This hypoxia-induced improvement in glucose levels could be explained by the positive action of glucose transporter-1, which upregulates intracellular glucose more so than normoxia (Serebrovska et al., 2019). However, the positive changes in glucose concentrations presented in the data of the present study stem from inclusion of short-term perceptually-regulated interval walking compared to longer term, fixed-intensity endurance and resistance training in hypoxia (De Groote et al., 2019). Identification of earlier metabolic benefits in response to hypoxic conditioning may increase adherence to exercise than a longer training program, and a perceptually-regulated intensity is likely to be more appropriate than a fixed-intensity for exercise tolerance (Ekkekakis & Lind, 2006). However, EE increased after training independently of environmental condition, whilst fuel metabolism was similar. Perhaps a greater training stimulus (i.e., longer weekly duration) is required to positively impact on EE and fuel metabolism parameters when in hypoxia compared to normoxia. To summarise, perceptually-regulated interval walking in hypoxia has larger positive adaptations on glucose concentrations than normoxia, but not EE and fuel metabolism.

Irrespective of condition, perceived mood change and exercise self-efficacy increased after training compared to before. No investigations have compared exercise-related sensations before and after hypoxic *versus* normoxic training in obese individuals. However, fixed-intensity interval training (60 × 8 s sprint at 90% $VO_{2PEAK}$/12 s recovery, 20 sessions in 5 weeks) in normoxic conditions has been reported as more enjoyable and easier for obese populations compared to moderate-intensity, continuous training (40 mins at 65% $VO_{2PEAK}$) (Kong et al., 2016a, Kong et al., 2016b). Due to the implementation of a perceptually-regulated exercise intensity in the current study, this may have mitigated the potential onset of hypoxic-induced negative mood (Lane et al., 2004) *via* matched physiological stress during training (i.e., HR). As a result, no negative perceptual responses occurred following training which likely contributes to maintaining motivation and increasing exercise adherence in obese individuals (Urdampilleta et al., 2012). Overall, similar improvements in perceived mood change and exercise self-efficacy result from perceptually-regulated interval walking in hypoxic and normoxic conditions.

### *7.6.3. Limitations and perspectives*

A single perceptually-regulated exercise intensity (RPE = 14) and $FiO_2$ (13.0%) were implemented in the current study in accordance with the findings of the previous study in this thesis (chapter 6). Potentially, alternative intensity (i.e., higher or lower RPE than 14) and $FiO_2$ targets (i.e., more or less severe than 13.0%) may lead to more favourable psycho-physiological responses during and following a short-term perceptually-regulated interval walking training period than those implemented here. Further, other anthropometric measures not assessed in the current study (i.e., waist: hip ratio, fat mass and muscle mass) that are pertinent for improved body composition should be assessed in future investigations.

## 7.7. Conclusion

In conclusion, matched perceptually-regulated interval walking velocities leads to similar levels of physiological stress (i.e., HR) and exercise-related sensations during short-term perceptually-regulated interval walking in hypoxia and normoxia in obese individuals. Whilst perceptually-regulated interval walking improves resting EE and exercise-related sensations compared to baseline irrespective of condition, improvements in resting blood glucose concentrations only occur in hypoxia. Significant weight loss was not achieved from either training condition. Short-term perceptually-regulated interval training in hypoxia could be implemented as an alternative strategy to current hypoxic conditioning recommendations as this leads to larger positive health improvements in obese individuals compared to normoxia.

### 7.8. Importance of findings for thesis

Short-term perceptually-regulated interval walking in hypoxia is a novel strategy that may accommodate positive physiological as well as perceptual responses to exercise in obese individuals compared to normoxia. Even though positive changes in important health markers, such as weight loss, improvements in EE and functional fitness, were not found in the current study, short-term perceptually-regulated interval walking in hypoxia did not negatively impact psycho-physiological responses in this population. Therefore, these findings contribute to the overall therapeutic usefulness of hypoxic conditioning in obese individuals.

# 8. General discussion

## 8.1. Thesis aims

The overall aim of this thesis was to investigate the psycho-physiological responses to active or passive hypoxic conditioning in adults with obesity. Previous studies have usually considered physiological (including metabolic and cardiovascular) responses to hypoxic conditioning in obese individuals, with a lack of investigation into perceptual responses. The approach utilised in the current thesis, combining measures of physiological and perceptual responses, and implementation of the perceptually-regulated exercise model is therefore unique. Indeed, characterising perceptual responses and exercise-related sensations would help design interventions to maximise training adherence in a cohort of obese individuals for better health outcomes. Further, transitioning from being sedentary (i.e., <1 h of moderate intensity exercise per week) (van der Ploeg & Hillsdon, 2017) to physically active is difficult to achieve in “at-risk” individuals. Therefore, this thesis firstly investigated:

- The acute effects of 60-min IHE sessions (passive hypoxic conditioning) including short, medium and long hypoxic/normoxic exposure cycles (matched total hypoxic and normoxic exposure time) *versus* a control on the magnitude and time course of psycho-physiological responses.

After determination of the optimal hypoxic/normoxic cyclical variation for larger psycho-physiological benefits in obese individuals, the next step was to introduce exercise. Prior to carrying this out with obese individuals, the first investigated:

- The effect of HIIT at a clamped RPE of 16 (typically used by athletes during HIIT) (Seiler & Sjursen, 2004) in hypoxia and normoxia on adjustments in running velocity and associated exercise-related sensations of trained runners.

This ‘*proof of concept*’ study provided initial insight into psycho-physiological responses to perceptually-regulated exercise intensities under the influence of hypoxia, preceding the next study which investigated:

- The acute effect of a 60-min perceptually-regulated (RPE = 14) interval walking (15 × 2/2 mins, derived from the main findings of the first study) session in hypoxic and normoxic conditions in obese individuals on physiological/metabolic responses, as well as exercise-related sensations and cognitive function. In addition, a third trial was carried out in normoxic conditions with a matched velocity selected in hypoxia to identify psycho-physiological responses in the absence of hypoxia.

The next logical step was to repeat the aforementioned interval walking protocol during a short-term training intervention for potentially larger and longer-term psycho-physiological benefits than a single session. Therefore, the final study investigated:

- The effects of a perceptually-regulated (RPE = 14) interval walking training intervention (eight sessions in two weeks) in hypoxic and normoxic conditions in obese individuals.

## 8.2. Main findings

The findings of study 1 (chapter 4) showed that long cycles of IHE (5 × 6 mins hypoxia/6 mins normoxia) led to greater desaturation (i.e., lower $SpO_2$ values) than short cycles (15 × 2 mins hypoxia/2 mins normoxia) during a single 60-min IHE session. However, perceived breathlessness was preserved more so following short compared to long IHE cycles. As such, short IHE cycles may be considered advantageous from a psycho-physiologically perspective (in terms of health and adherence factors) for obese individuals.

Study 2 (chapter 5) concluded that trained runners adjusted to a progressively slower running velocity during a single, perceptually-regulated HIIT session (4 × 4-min at RPE = 16, 3-min recoveries) and even more so in hypoxia *versus* normoxia. This led to similar levels of physiological stress during (i.e., matched HR and muscle oxygenation haemodynamics) and cognitive function after HIIT between conditions. When exposed to hypoxia, however, exercise-related sensations were negatively impacted before (i.e., perceived recovery and motivation) and after (i.e., perceived breathlessness, limb discomfort and pleasure) HIIT intervals.

Study 3 (chapter 6) reported that obese individuals adjusted to a progressively slower walking velocity during a single, perceptually-regulated interval walking session more so in hypoxia *versus* normoxia (15 × 2 mins at RPE = 14, 2-min recoveries, ratio optimised from study 1, chapter 4). Compared to normoxia, perceptually-regulated interval walking in hypoxia induced a greater level of physiological stress (i.e., higher HR and lower muscle oxygenation) yet lower exercise-related sensations (i.e., perceived limb discomfort). Interestingly, at the same velocity in the absence of hypoxia, exercise-related sensations were matched with lower levels of physiological stress compared to when obese individuals were in hypoxia. The next step was to implement a training intervention for potentially further positive effects.

Study 4 (chapter 7) revealed no differences in treadmill velocity and HR during a short-term perceptually-regulated interval walking intervention between hypoxic and normoxic conditions (15 × 2 mins at RPE = 14, 2-min recoveries, 8 sessions in 2 weeks). Improvements in resting blood glucose concentrations were found following hypoxic compared to normoxic training, with no differences in body mass, BMI and blood pressure following training. Training-induced improvements in resting energy expenditure, mood state, and exercise-self efficacy occurred irrespective of condition.

## 8.3. Transitioning from passive to active hypoxic conditioning

At present, moderate-intensity physical activity (between 150–250 mins/week) is suggested to promote weight loss (i.e., a decrease of ≥3% in total body weight), whilst greater amounts of physical activity (>250 mins/week) will likely lead to clinically significant weight loss (i.e., a decrease of ≥5% in total body weight) (Donnelly et al., 2009). It should be highlighted that one of the most difficult aspects of weight loss is initiating the process, whether that be due to physiological, psychological or logistical constraints (Johnson & Eaves, 2013). Kushner (2014) reported that individuals beginning a weight loss strategy should be counselled on evidence-based lifestyle approaches that include diet, physical activity and behaviour change therapies. Given the ever-increasing obesity rates, it could be suggested that some current weight loss strategies (i.e., exercise training, dietary manipulation), taking into account the initial, loss and maintenance phases, are lacking efficiency. The series of experimental studies presented in this thesis offer an alternative strategy to current paradigms for improving psycho-physiological responses and potentially promoting weight loss in obese individuals.

A single passive hypoxic conditioning session (IHE), regardless of the cycle duration, induces significant physiological stress (i.e., decreased $SpO_2$) compared to normoxia, whilst perceived breathlessness is preserved to a greater extent following short *versus* long cycles of IHE in obese individuals (study 1, chapter 4). Over a longer period of time (1 h per day, 5 days per week, 4 weeks), Wang et al. (2007) demonstrated that passive hypoxic conditioning ($FiO_2$ = 15.0%) led to increases in pulmonary ventilation and $VO_2$ compared with normoxia in sedentary men during a maximal exercise performance task. Additionally, passive hypoxic conditioning (3 h per day for one week, $SpO_2$ clamp = ~80%) significantly elevated EE and fat over carbohydrate oxidation compared to normoxia in overweight and sedentary males (Workman & Basset, 2012). Although weight loss was not assessed in these studies, the collective positive responses (i.e., increased physiological and metabolic stress and preserved perceptual responses) to passive hypoxic conditioning are achieved in the absence of physical activity. Notably, initiating regular physical activity is not straightforward for most individuals who are currently obese and/or sedentary. Taken together, it could be suggested that selecting the optimal hypoxic and normoxic cycle for maximising the psycho-physiological responses during passive hypoxic conditioning could lead to better psycho-physiological responses (i.e., larger EE) when hypoxic exposure is combined with exercise (i.e., active hypoxic conditioning).

Findings from study 3 (chapter 6) of the current thesis show that a single active hypoxic conditioning session (15 × 2 mins walking at RPE 14/2 mins resting, $FiO_2 = 13.0\%$) resulted in decreases in treadmill velocity compared to normoxia during intervals. This provided larger levels of physiological stress (i.e., increased HR, decreased $SpO_2$ and muscle oxygenation) and lower indices of exercise-related sensations (i.e., perceived limb discomfort) during hypoxia in reference to normoxia. When carried over a short-term (eight sessions over two weeks) training intervention, the perceptually-regulated intensity is matched between hypoxic conditioning and normoxia during interval walking (study 4, chapter 7). Within the literature, numerous studies have reported a lower external workload (i.e., treadmill velocity, cycling power output) for a similar internal physiological stress (i.e., HR) during short-term (nine 60-min sessions in three weeks) (Fernandez-Menendez et al., 2018) and chronic active (seven to twelve 30–60 mins sessions in three to four weeks) (Pramsohler et al., 2017, Wiesner et al., 2009) hypoxic conditioning compared with normoxia. Albeit similar to normoxia, weight loss has also been reported following chronic active hypoxic conditioning (60–90 mins continuous cycling at 60–65% $VO_{2MAX}$, three times per week for four to eight weeks, $FiO_2 = 15.0\%$) (Kong et al., 2013, Netzer et al., 2008, Wiesner et al., 2009). Therefore, the workload required to achieve the degree of physiological stress for positive adaptations and promotion of weight loss is less pronounced when in hypoxia *versus* normoxia and when exercising continuously compared to interval training. In study 4 (chapter 7), lower workloads when in hypoxia to match a perceptually-regulated target (i.e., RPE = 14) may not have been selected as the said target was maintained over the training intervention. It has been shown that over a similar training intervention (60 mins continuous walking at a preferred walking velocity, three sessions per week for three weeks, $FiO_2$ = 14.5%), obese adults walked progressively faster week after week in hypoxia (+8%), but the velocity remained slower than normoxia (–9%) (Fernandez-Menendez et al., 2018). The maintenance in RPE target within study 4 (chapter 7) of the current thesis may explain the discrepancy between these findings and those within the literature (Fernandez-Menendez et al., 2018). Collectively, lower external workloads are selected during chronic hypoxic conditioning at a moderate, continuous fixed-intensity compared to normoxia, but these adjustments do not occur during short-term, perceptually-regulated in interval walking.

## 8.4. Acute and short-term active hypoxic conditioning

Study 2 (chapter 5) showed that trained runners adjusted to a progressively slower running velocity to maintain an RPE of 16 during a single session of active hypoxic conditioning compared to normoxia. Obese individuals also did the same to match an RPE of 14 (study 3, chapter 6). However, during short-term active hypoxic conditioning, the perceptually-regulated intensity of obese individuals to match an RPE of 14 was not different to normoxia (study 4, chapter 7). This may be somewhat surprising at first, given that individuals carried out eight 60-min interval walking sessions in two weeks at an intensity considered to be '*somewhat hard*' to '*hard*'. The added stimulus of hypoxia made it tenable that the walking velocity selected would be slower during hypoxic conditioning *versus* normoxia, as per the hypotheses. Additionally, it has been shown that relatively lower fixed (Haufe et al., 2008, Wiesner et al., 2009) and self-selected (Fernandez-Menendez et al., 2018) exercise intensities in hypoxia than normoxia provide similar levels of physiological stress (i.e., HR), suggestive of a similar perceptual load (i.e., RPE). A decreased velocity during short-term active hypoxic conditioning (15 × 2 mins walking at RPE = 14, 2-min recoveries, 8 sessions in 2 weeks) respective to normoxia did not occur, unlike acute active hypoxic conditioning, due a potential lack of fatigue. It could be argued that as participants were able to perceptually-regulate the intensity, they minimised the onset of central and/or peripheral fatigue during a short-term intervention (Hawley, 2008) when in hypoxia and normoxia. This may not have occurred if the exercise intensity was fixed, and thus over-inducing physiological stress in hypoxia compared to normoxia (Heinonen et al., 2016). Overall, exercise training (continuous or interval) in hypoxia at a matched or lower workload induces similar or greater levels of physiological stress than normoxia (studies 2 and 3, chapters 4 and 5, Haufe et al., 2008, Wiesner et al., 2009). The requirements of a lower workload during hypoxic conditioning would likely decrease the effort required for obese individuals to achieve sufficient physiological stress during exercise compared to normoxia, and perhaps promote greater adherence. For the final study presented in this thesis (study 4, chapter 7), power analyses revealed that 14 participants were required per group. As the recruited number of obese individuals was lower than the requirement for statistical power ($\alpha$ = 0.05 and $\beta$ = 0.8), with a larger participant cohort, differences in perceptually-regulated interval walking may have been realised between environmental training conditions during short-term active hypoxic conditioning.

In regard to the transition of acute and short-term active hypoxic conditioning into the real-world, it could be argued that the negative exercise-related sensations to a single active hypoxic conditioning session *versus* normoxia may outweigh the physiological benefits. Based on the findings presented with this thesis, it appears that active hypoxic conditioning is initially perceived as generally more difficult even when the exercise intensity is perceptually-regulated (study 2, chapter 6). Nevertheless, this negative response later subsides (i.e., exercise-related sensations are not different between conditions) when a series of perceptually-regulated interval walking sessions are completed (study 4, chapter 7). Similar findings were also found by Brocherie et al. (2017), whereby elite field hockey players performed a repeated-sprint protocol (4 × 5 × 5 s maximal sprints, 25 s passive recovery, 5 min rest, 6 sessions in 2 weeks) in hypoxia ($FiO_2$ = 14.5%) *versus* normoxia. It was found that exercise-related sensations (i.e., perceived overall peripheral discomfort, breathlessness and lower-limb discomfort) were negatively impacted during the first repeated-sprint session in hypoxia compared to normoxia. However, from the second to the final session there were no differences in exercise-related sensations between conditions. Negative exercise-related sensations to an acute active hypoxic conditioning session could be attributed to increases in ventilation upon initial exposure to hypoxia (Aliverti et al., 2011), and quicker elevations in blood lactate concentrations (Amann et al., 2010). Taken together, although exercise-related sensations are negatively impacted upon initiation of active hypoxic conditioning (i.e., during a single session or first session of an intervention), continuation of regular active hypoxic conditioning normalises these effects. This highlights the tolerable nature of hypoxia in trained and obese individuals, suggestive of further therapeutic benefits.

## 8.5. Perceptually-regulated exercise model

As described in the literature review (chapter 2), a perceptually-regulated exercise intensity may be more appropriate for obese individuals when carrying out exercise than a fixed-intensity. This is possibly due to the greater pleasure felt during walking when the pace is self-regulated compared to an imposed intensity (Ekkekakis & Linds, 2006). However, little is known regarding the effects of hypoxia upon the perceptually-regulated exercise model for obese individuals. The results of the current thesis show that both trained runners and obese individuals perceptually-regulated to a progressively slower treadmill velocity when ambulating in hypoxic compared to normoxic conditions during a single interval session (study 2, chapter 5 and study 3, chapter 6). For individuals who are obese, this finding alone is particularly beneficial given that a lower external workload (i.e., treadmill velocity) would likely decrease the impact put through joints that are already under excessive strain compared to normal-weight individuals during foot contact (Girard et al., 2016). Interestingly, the physiological stress was larger (i.e., higher HR, lower muscle oxygenation) during hypoxia compared to normoxia in obese individuals (study 3, chapter 6). However, utilisation of the fixed-intensity exercise model during acute (15 × 1-min high-intensity exercise at 75% $HR_{MAX}$,1-min passive recovery, $SpO_2$ clamp = 76%) hypoxic conditioning has also reported a relatively lower intensity yet higher physiological stress in hypoxia than normoxia (Chacaroun et al., 2018). Similar findings have also been reported during chronic hypoxic conditioning (60 mins cycling at 60% $VO_{2MAX}$, three times per week for four weeks, $FiO_2$ = 15.0%) (Wiesner et al., 2009). Overall, the perceptually-regulated exercise intensity model when utilised during hypoxic conditioning induces similar responses in terms of physiological stress as the fixed-intensity exercise model.

However, it is important to note that perceived limb discomfort was significantly lower during acute active hypoxic conditioning (i.e., interval walking) at a perceptually-regulated exercise intensity of obese individuals (study 3, chapter 6). In fact, the decreases in limb discomfort were similar between acute hypoxic conditioning and in the absence of hypoxia at the same velocity compared to perceptually-regulated interval walking in normoxia. Based on the findings of the current thesis, the perceptually-regulated exercise model induces physiological stress for a lower perceptual load of obese individuals, which is further enhanced when carried out in hypoxia. Even though exercise-related sensations such as perceived limb discomfort were not assessed in the studies by Chacaroun et al. (2018) or Wiesner et al. (2009), it could be argued that perceptually-regulated exercise model could promote collectively better acute psycho-physiological responses than a fixed-intensity in obese individuals. Nevertheless, the final study of this thesis showed that the perceptually-regulated exercise intensity (i.e., treadmill velocity) and subsequent physiological stress as well as perceptual responses were not different during training between hypoxic conditioning and normoxia (study 4, chapter 7). This finding is inconsistent with the literature as it has been concluded elsewhere that chronic active hypoxic conditioning at a fixed and perceptually-regulated intensity is carried out at a lower workload than normoxia (Fernandez-Menendez et al., 2018, Haufe et al., 2008, Wiesner et al., 2009). It could be suggested that this discrepancy is due to implementation of regular interval walking sessions (15 × 2 mins walking at RPE 14, 2 mins resting, 8 sessions over 2 weeks) rather than exercise that is continuous in nature. As such, the extent to which obese individuals adjust the exercise intensity to maximise stability and minimise the external workload is reduced during shorter bouts of exercise with interspersed recovery (Malatesta et al., 2009). Overall, short-term hypoxic conditioning (i.e., interval walking) at a perceptually-regulated exercise intensity is not different to normoxia, whilst inducing similar levels of physiological and perceptual stress.

## 8.6. Psycho-physiology trade off

Intuitively, being obese negatively impacts both psychological and physiological factors of health (Carels et al., 2007). Therefore, health-focused interventions should aim to improve psycho-physiological responses rather than one function alone to target the implications of obesity on multiple systems of the human body. The findings of the experimental studies featured in the present thesis have uncovered psycho-physiological responses to hypoxic conditioning in obese individuals. Initially, the findings of the first study (chapter 4) revealed that shorter cycles of hypoxia and normoxia decreased $SpO_2$ compared to a control (i.e., continuous normoxia) session, whilst also preserving levels of perceived breathlessness in reference to longer cycles. The subsequent studies that included obese individuals (study 3, chapter 6 and study 4, chapter 7) utilised short cycles for interval walking during active hypoxic conditioning based on the aforementioned study. If a combination of psycho-physiological responses were not incorporated in the current thesis, $SpO_2$ responses to passive hypoxic conditioning would have indicated that long hypoxic and normoxic cycles should be implemented during active hypoxic conditioning. Within the literature, it has been shown that very short duration HIIT (4–6 × 30 s maximal effort, 4 mins recovery, six sessions in two weeks) is time-efficient for inducing physiological adaptations such as muscle oxygenation in healthy young men compared to moderate-intensity cycling (90–120 mins) (Gibala et al., 2006). In obese individuals, the same short duration HIIT protocol has shown to reduce metabolic and vascular risk factors (Whyte et al., 2010) and circulatory function (Trilk et al., 2011) compared to moderate-intensity continuous exercise. However, it has been argued that psychological factors highlight that short duration HIIT evokes negative post-exercise affects, which then diminishes motivation and adherence (Hardcastle et al., 2014). Therefore, regular completion of this exercise format in particular, regardless of the positive physiological effects, is at a premium. Overall, due to the studies presented in the current thesis determining both psychological and physiological factors to hypoxic conditioning, it could be argued that the short duration perceptually-regulated interval walking implemented here is optimised for positive psycho-physiological responses of obese individuals.

## 8.7. Hypoxic dose

For hypoxic conditioning, a lower $FiO_2$ than normoxia *via* increased nitrogen filtration was utilised. The $FiO_2$ provided during passive hypoxic conditioning (study 1, chapter 4) was equal to 12.0%, whilst active hypoxic conditioning for trained runners was 15.0% (study 2, chapter 5), and 13.0% for obese individuals (study 3, chapter 6, and study 4, chapter 7). These values were selected based on the current literature (Navarette-Opazo & Mitchel, 2014), and through pilot testing of each experimental study. Hypoxemia typically occurs during exposure to oxygen-deprived environments, and is defined as an $SpO_2$ <90% (Basnet et al., 2006). Hypoxemia induced through active hypoxic conditioning for both trained runners and obese individuals appeared as expected ($SpO_2$ = ~80–85%). However, during passive hypoxic conditioning including short cyclical exposure, the extent of hypoxia-induced hypoxemia could be questioned due to smaller decreases in $SpO_2$ compared to normoxia (~90–94%).

The $SpO_2$ of obese individuals was lower during IHE compared to normoxia (-6%), whilst longer cycles decreased $SpO_2$ further compared to medium (-3%) and short (-4%), as shown in study 1 of the current thesis (chapter 4). Interestingly, when exposed to acute passive hypoxic conditioning ($FiO_2$ = 12.0%, 20-min continuously), decreases in $SpO_2$ of obese, pre-diabetic individuals are more pronounced (-19%) (Serebrovska et al., 2017). Unlike Serebrovska et al. (2017), it could be argued that the passive hypoxic conditioning protocols employed in the current thesis (study 1, chapter 4) did not reach hypoxemia. It has been suggested that the severity of hypoxemia induced during hypoxic conditioning modulates physiological responses (Amann et al., 2007). Therefore, the hypoxemia induced during the first study presented in this thesis led to differences in $SpO_2$, albeit small, between short, medium and long cycles of hypoxia and normoxia. In other studies, a clamped $SpO_2$ (~80%) for up to 3 hours has been utilised to ensure hypoxia-induced hypoxemia during passive hypoxic conditioning (Chacaroun et al., 2017, Costalat et al., 2017, Workman & Basset, 2012). In summary, greater hypoxemic states have been induced with longer single exposure times, and alternative methods to what have used been used in the studies presented in this thesis (i.e., clamped $SpO_2$). However, the findings of the current thesis highlight the trade-off between psycho-physiological responses to a single hypoxic dose during passive hypoxic conditioning in obese individuals utilising a fixed $FiO_2$ and identified the optimal cycle duration of hypoxia and normoxia for acute psycho-physiological responses in obese individuals.

In regard to the hypoxic dose, recent publications have highlighted therapeutic ranges of $FiO_2$ for diseased populations. '*Low dose*' hypoxic conditioning with modest hypoxia ($FiO_2$ = 9.0–16.0%) and few cycles (3–15) may be a simple, safe and effective treatment with considerable therapeutic potential (Navarrete-Opazo & Mitchell, 2014). Further, adaptive responses occur during low dose hypoxic conditioning ($FiO_2$ >16.4%), and in individuals without severe illnesses (Burtscher et al., 2012). The main finding reported from the first study of this thesis (chapter 4) is in agreement with the recommendations of Navarrete-Opazo & Mitchell (2014), where it was shown that more frequent (15) and shorter (2 mins) cycles of hypoxia lead to better psycho-physiological responses (i.e., decreased $SpO_2$ and preserved perceptions of breathlessness) compared to less frequent and longer cycles of hypoxia. Therefore, it could be argued that this hypoxic conditioning (15 × 2 mins hypoxia/2 mins normoxia, $FiO_2$ = 12.0%) could be implemented safely and effectively in a practical setting (i.e., gym or clinic). However, these findings are reported from individuals with stage I obesity, potentially different psycho-physiological responses may occur in various populations (i.e., stage II and III obesity).

### 8.8. Real-world availability and application of hypoxic conditioning

Over the last 15–20 years, there has been a surge in research regarding hypoxic conditioning as a therapeutic strategy. In the first instance, data from altitude sojourns (Westerterp-Platenga et al., 1999) and residence (Voss et al., 2013) showed that this led to weight loss compared to sea level residency. In today's society, there are several recognised commercial gyms providing hypoxic conditioning to the general population across the UK. Potentially, the 61% of the general population considered as overweight and obese (NHS, 2018) may benefit in relation to psycho-physiological responses and body mass changes following hypoxic conditioning.

However, the logistical and economic considerations of hypoxic chambers will likely impede on installations and setup. It could be suggested that greater use of hypoxic conditioning will be made if more affordable and portable (i.e., for easier home use) setups could be developed in the future. Further, the cost-effectiveness of hypoxic conditioning for improving psycho-physiological responses in obese populations is not understood at present. Hypoxic conditioning may have the potential to be more cost-effective than other lifestyle interventions (i.e., gym usage, behavioural therapy and drugs), ranging between £473–7200 per quality-adjusted life-year gained (Loveman et al., 2011). Overall, the real-world availability of hypoxic conditioning should be of greater consideration given the positive research findings published recently to provide more opportunities to those in the general population to utilise this strategy. Alternatively, how hypoxic conditioning is currently implemented could be evaluated for further improvements compared to normoxic training. Study 3 (chapter 6) of the current thesis highlighted time-dependent increases in fat oxidation following a single 60-min perceptually-regulated interval walking session in hypoxia ($FiO_2$ = 13.0%), which was maintained for up to 60 mins after. Further, study 4 (chapter 7) showed time-dependent trends for a higher EE following (3 ± 2 days after the final session) two weeks of active hypoxic conditioning (8 × 60-min perceptually-regulated interval walking, $FiO_2$ = 13.0%). Four weeks after completing an active hypoxic conditioning programme (aerobic intervals: 3 mins at 90% maximal power output, 3 mins at 55–65% maximal power output, sprint intervals: 30 s all out: mins at 55–65% maximal power output, 3 sessions per week for 12 weeks, $FiO_2$ = 17.2%), overweight and obese women continued to lose abdominal fat compared to normoxic training (Camacho-Cardenosa et al., 2019). Although the continuation in positive responses to hypoxic conditioning only concerns one assessment of body composition, this could highlight the prolonged beneficial effects following short-term hypoxic conditioning. However, further psycho-physiological measures are required to validate this claim.

An alternative to hypoxic conditioning utilised in the current thesis (i.e., IHE or active) surrounds implementation during residency. A recent study reported improved glucose tolerance of individuals with Type II Diabetes following 14 nights of home-based, passive hypoxic conditioning ($FiO_2$ = 15.0%) (Marlatt et al., 2019). This finding should be of interest given the high risk of developing Type II Diabetes when obese (Gambineri & Pelusi et al., 2019). Naturally, the practical home-based nature of this study design is novel, and may provide metabolic health improvements without significant lifestyle changes compared with starting an exercise programme or dietary intervention. As a lack of time is commonly cited as a barrier to exercise completion and adherence (Reichert et al., 2007), passive hypoxic conditioning during sleep could be a viable option for further psycho-physiological responses in obese populations similar to that of the protocol presented in study 1 (chapter 4) of the current thesis. Although blood glucose concentrations were not measured in response to passive hypoxic conditioning (study 1, chapter 4), significant reductions were reported in this parameter following short-term active hypoxic conditioning (study 4, chapter 7). However, the required commitment to short-term active hypoxic conditioning is greater than short-term passive hypoxic conditioning. Overall, the development of methods for implementing hypoxic conditioning and refining of best practice is informed by growing evidence.

In clinical settings, the use of hypoxic training is still in its infancy. Therefore, recommendations for implementation of best practice are not firm at present. However, it could be considered whether the '*buy-in*' from health governing bodies and their institutions, clinicians and obese populations, to an extent, exists when implementing hypoxic training to benefit health. A handful of studies investigating the positive physiological effects in response to hypoxic training have been carried out in clinical settings, such as an immersive residential camp (Kong et al., 2013) or a hospital inpatient ward (Pramsohler et al., 2017). It could be possible for participants to respond more positively to hypoxic conditioning if they are in a more habitual environment compared to a laboratory (Korman et al., 2016). This type of study may be informative for the timing of implementing hypoxic conditioning relative to surgical procedures and reduce the economic costs of other alternative therapies.

## 8.9. Limitations

The methodology, findings and interpretations of the experimental studies within this thesis naturally include limitations. These can be found outlined below:

- Across all experimental studies composed within this thesis, participants were instructed to refrain from caffeine and alcohol for ≥48 h prior to each experimental trial and maintain a habitual diet whilst enrolled onto the study, as described in chapter 3. Therefore, although advised to maintain their diet, the total daily calorie intake and meal timing may have varied between participants. Further, physical activity outside of experimental trials/exercise sessions was not quantified. Overall, although unlikely, there is potential that participants may have increased their calorie intake or became more/less active during their time spent enrolled onto a study, which could have impacted the findings reported regardless of the extent of advice given by the investigators (particularly study 4, chapter 7).
- During passive and active hypoxic conditioning, physiological and perceptual responses were recorded. However, cardio-metabolic health assessments (i.e., EE, fat and glucose metabolism) were not carried out during, rather pre- and post-hypoxic conditioning. Cardio-metabolic health assessments during passive and active hypoxic conditioning would have provided an additional insight to the current findings presented into the metabolic stress induced by hypoxia. Duncan (2019) showed elevated EE during 45-min continuous passive hypoxic conditioning ($FiO_2$ =12.0%) compared with normoxic rest in physically active individuals. It could be argued that

this type of assessment in the studies featuring in the current thesis would have provided further, potentially positive (i.e., increased EE), indications of the therapeutic benefits of hypoxic conditioning in obese populations.

- Where perceptually-regulated exercise was implemented in the experimental studies of this thesis, a single RPE target for obese individuals (RPE = 14) and trained runners (RPE = 16) was utilised. Pilot testing revealed that an RPE of 14 was most appropriate in terms of intensity for obese individuals carrying out the specified exercise training (i.e., interval walking). For trained runners, an RPE of 16 is consistently maintained irrespective of the interval duration during running (Seiler & Sjursen, 2004). Nonetheless, it is possible that alternative RPE targets during perceptually-regulated interval training may have provided further positive psycho-physiological responses (i.e., larger physiological stress without negatively impacted exercise-related sensations) to that already achieved in the current thesis when in hypoxia compared to normoxia.
- Although a strong argument in chapter 3 for inclusion of BMI assessment as a criterion of eligibility for the experimental studies recruiting obese volunteers is presented, others may argue that there are better alternative assessments. The use of bioelectrical impedance devices to determine fat mass quantities have been validated previously (Barreira et al., 2012, Goldfield et al., 2006). Also, waist: hip ratio takes into consideration visceral fat tissue which may provide further indication of cardio-metabolic health (Song et al., 2013). It is unlikely that the conclusions presented in this thesis would be different if alternative assessments of body composition were utilised, but the aforementioned assessments may have provided further insight to potential changes of segmental tissue (i.e., fat and muscle mass locations) in response to hypoxic conditioning.

- In experimental studies 1, 3 and 4 (chapters 4, 6 and 7), the participant cohorts identified as obese and completed the studies are relatively small (8–16). Importantly, the pre-determined level of statistical power was calculated and met prior to participant dropout for these studies. This may explain the lack of statistical differences in some psycho-physiological parameters assessed within these studies in response to hypoxic conditioning. Larger participant cohorts may have highlighted greater, and statistically significant in some instances, differences in psycho-physiological responses to hypoxic conditioning in obese individuals.
- The entire thesis relates to obese individuals, however, it should be highlighted that this relates directly to stage I obesity (BMI = 30–34.9 kg/m). Recruited individuals were within this category due to a likely increased benefit (i.e., physically able to exercise) and decreased risk (i.e., less physical risks during exercise) compared to stage II and III obesity. It is likely that individuals within the multiple stages of obesity would have responded differently (i.e., potentially larger changes in perceptions and exercise-related sensations) to hypoxic conditioning in relation to psycho-physiology due to their respective initial fitness level.

## 8.10. Future research direction

Given the already established positive findings of hypoxic conditioning for improving psycho-physiological responses in obese populations presented in the literature review and experimental studies of this thesis, there are specific avenues for future research to take to build upon this.

Firstly, to date only one study has investigated body composition responses to active hypoxic conditioning after a period of '*detraining*' (i.e., no training with a retention measurement) (Camacho-Cardenosa et al., 2019). The main finding showed that abdominal fat mass continued to decrease compared to the overweight and obese females who completed normoxic exercise. This type of investigation (i.e., inclusion of retention measurements) which was not included in the current thesis could provide further insight regarding the chronic effects on cardio-metabolic health (i.e., EE) and weight loss (i.e., segmental and total body mass) of hypoxic conditioning as a therapeutic strategy for obese individuals. This may further demonstrate the potential sustainability of hypoxic conditioning.

Secondly, many studies, including ours, implement 3–4 hypoxic conditioning sessions per week for 2–8 weeks which has typically led to improved cardio-metabolic health (i.e., increased EE, decreased blood pressure). However, there has been little-to-no consideration for other lifestyle factors, such as daily physical activity levels. In line with this, weight loss and then maintenance may have contributions from a higher daily physical activity, lower dietary intake and/or a greater daily EE (Ostendorf et al., 2019). As such, assessment of daily physical activity *via* wearable technological devices and monitoring of diet during hypoxic conditioning programmes should be considered in the future.

Thirdly, although the data presented in this thesis focuses on psycho-physiological responses, measurements of biomechanical data (i.e., kinetics, kinematics and spring-mass model characteristics) were made during study 2 (chapter 5) *via* force plates located underneath the treadmill belt participants ran on during perceptually-regulated HIIT. Theoretically, the progressively slower perceptually-regulated velocities during active hypoxic conditioning in reference to normoxia may preserve vertical ground reaction forces put through lower limb joints upon ground contact *via* a lower external workload (Girard et al., 2016). For obese individuals, these potential findings may infer that the stress put through joints and limbs that are already strained is decreased in hypoxia due to lower external workloads and eventually increase exercise enjoyment and adherence.

Next, the studies presented in this thesis were carried out in laboratory environments and during passive and active hypoxic conditioning sessions. As eluded to in the current chapter, where and how hypoxic conditioning is currently being implemented could be further optimised for obese individuals. For example, studies carried out in a clinical setting (i.e., a hospital ward) may promote larger psycho-physiological gains compared to laboratory environments due to potentially greater ecological validity. In a similar fashion to passive hypoxic conditioning, preliminary data has reported that sleeping in a hypoxic environment has positive actions on glucose tolerance of individuals with Type II Diabetes (Marlatt et al., 2019). Based on this data and the known common factors between individuals who are obese and those with Type II Diabetes, beneficial responses could also be found following this type of intervention in individuals who are obese, but this has yet to be investigated to date.

Lastly, the interval duration of work/rest in studies 3 and 4 of this thesis (chapters 6 and 7) was selected based on the findings of study 1 (chapter 4). However, it could be possible that psycho-physiological responses to active hypoxic conditioning could be further optimised with different interval durations of work/rest. Rather than duration-based, interval training could be individually optimised to meet a specified level of metabolic stress. For example, obese individuals could exercise over short, intense bouts with the target of expending ~50–75 kcal per bout and repeat this until ~500 kcal are expended in total across one session. It is expected that the duration to reach this EE would be shorter in hypoxic compared to normoxic conditions giving the additional stress on the human system (Heinonen et al., 2016). Overall, investigations should aim to maximise the extent of physiological and metabolic stress induced during exposure to hypoxia, without negatively impacting perceptual responses, such as exercise-related sensations, compared to exercise in normoxia. This would likely increase and maintain adherence to active hypoxic conditioning.

## 8.11. Conclusions

In conclusion, this thesis has highlighted the importance of psycho-physiological responses to hypoxic conditioning in obese individuals. Initially, a psycho-physiologically optimised cyclical variation exposure to hypoxia at rest was determined (short, frequent cycles), and then implemented during perceptually-regulated exercise under hypoxia versus normoxia. Progressively lower external workloads in hypoxia achieve similar, if not greater, levels of acute physiological stress in obese individuals compared to normoxia. Further, this is in accordance with a lower perceptual effort. Following short-term active hypoxic conditioning, positive influences on key metabolic markers relating to obesity-associated co-morbidities (i.e., decreased resting glucose concentrations) compared to normoxia, with similar improvements in perceptual responses (i.e., perceived mood state and exercise self-efficacy) are realised. Overall, implementation of a perceptually-regulated exercise model within active hypoxic conditioning may provide further acute and short-term benefits than normoxia. Given the current rising rates of obese populations in the UK, collectively, these findings indicate that a) a combination of physiological and psychological responses are important when implementing hypoxic conditioning in obese individuals, and b) when psycho-physiologically optimised, passive and active hypoxic conditioning benefits multiple health factors of obese individuals.

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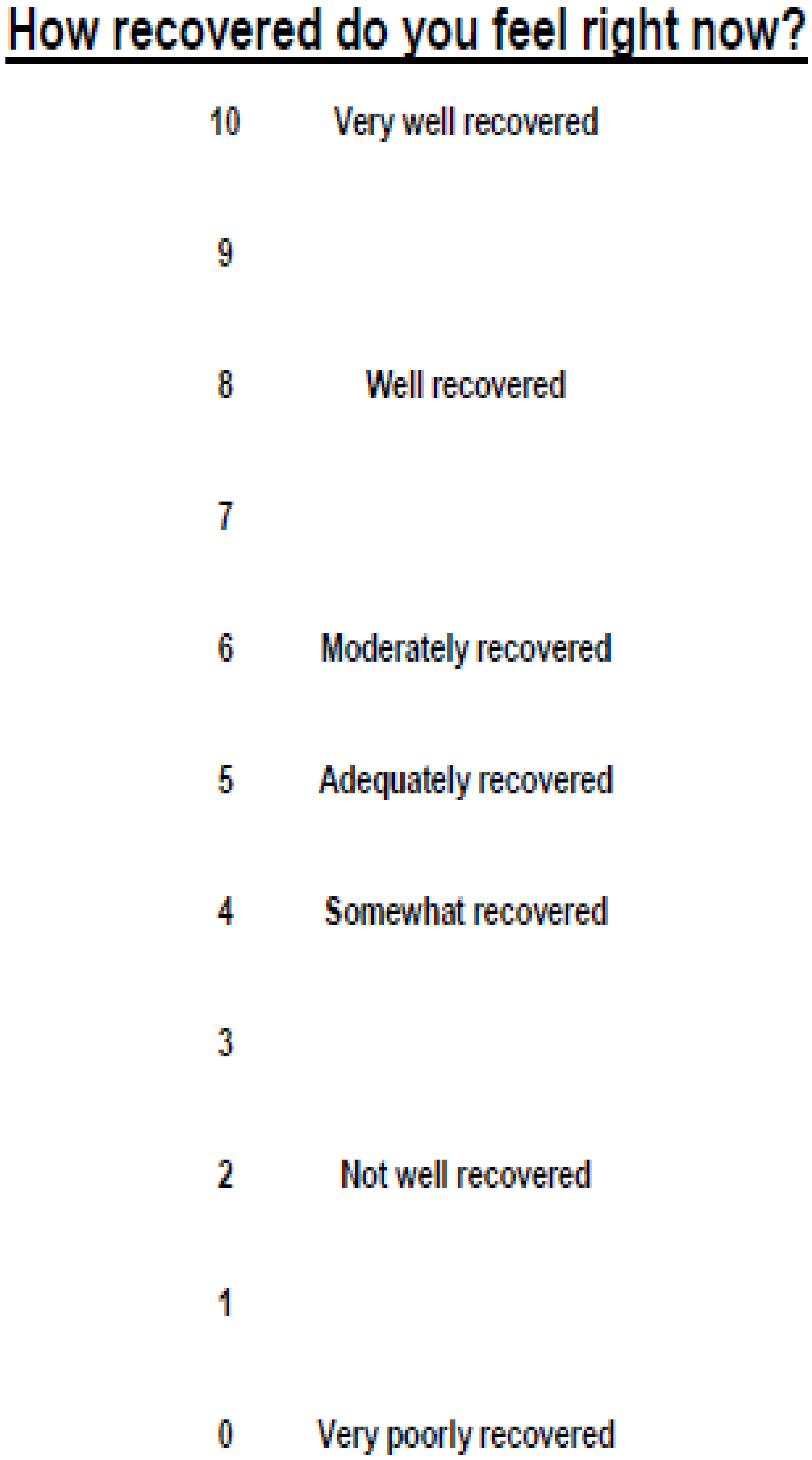
## Appendices

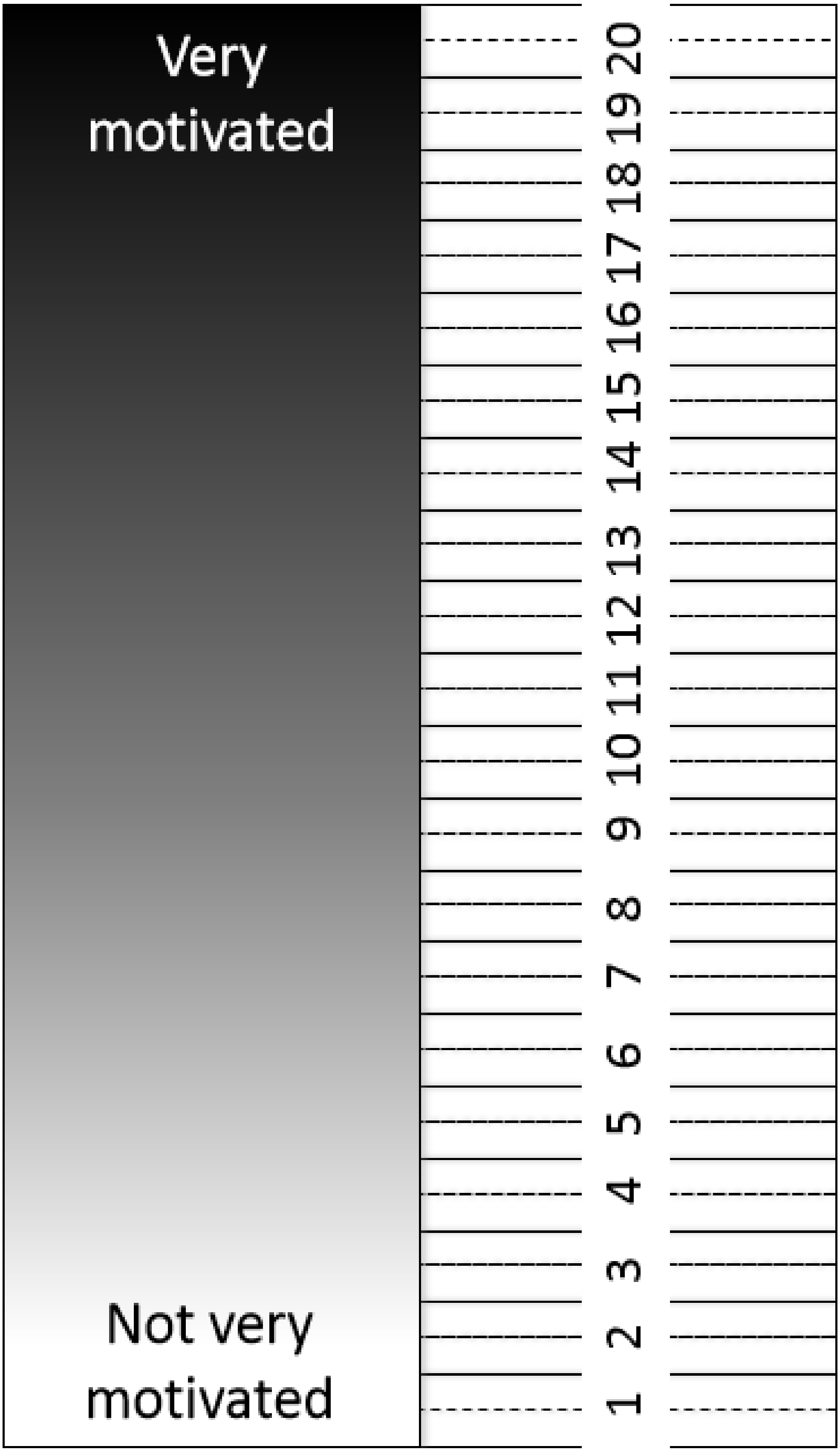
**Appendix 1** Perceived recovery scale (Laurent et al., 2010).



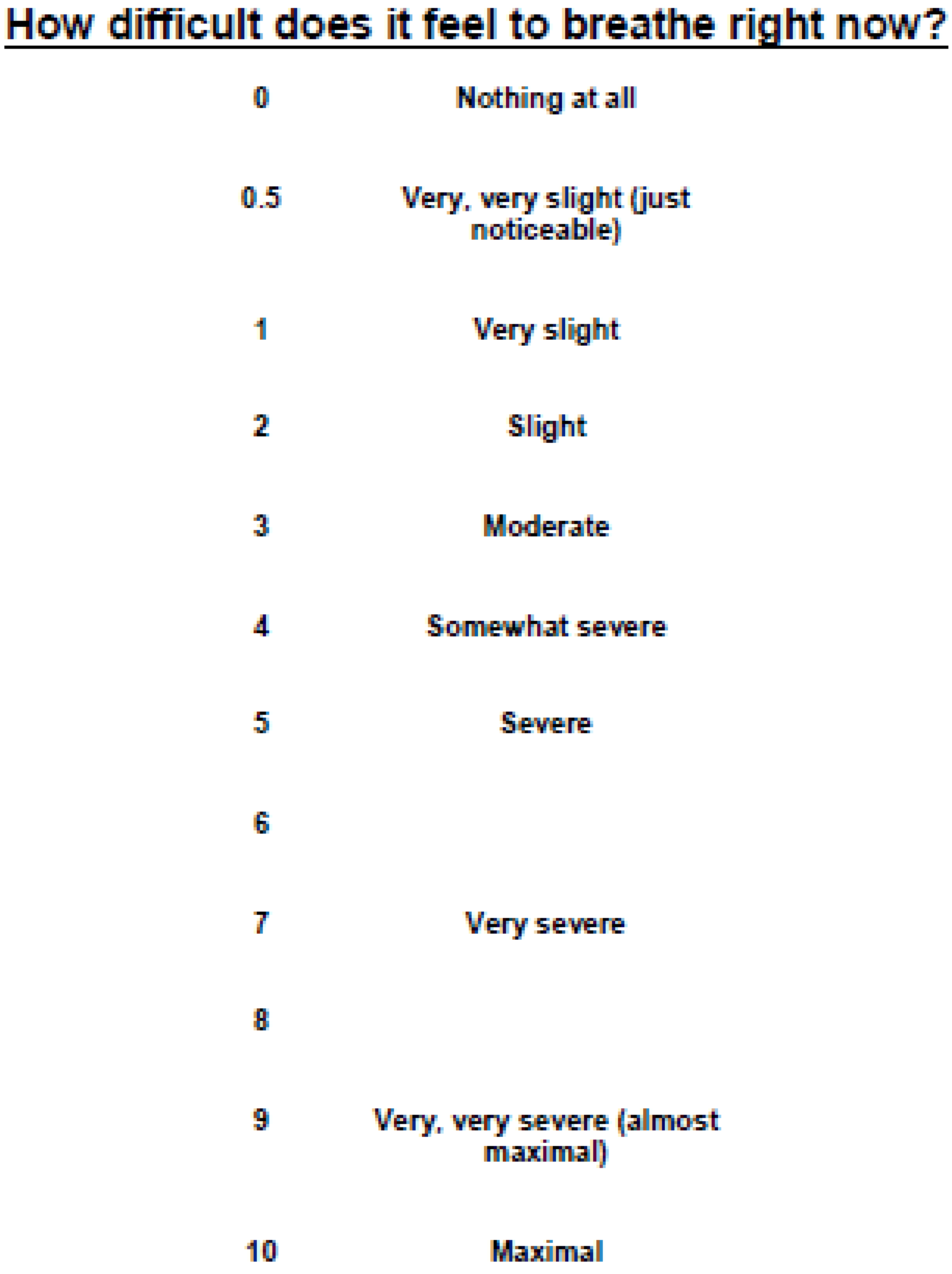
How recovered do you feel right now?

| | |
|---|---|
| 10 | Very well recovered |
| 9 | |
| 8 | Well recovered |
| 7 | |
| 6 | Moderately recovered |
| 5 | Adequately recovered |
| 4 | Somewhat recovered |
| 3 | |
| 2 | Not well recovered |
| 1 | |
| 0 | Very poorly recovered |

**Appendix 2** Perceived motivation scale (Crewther et al., 2016).



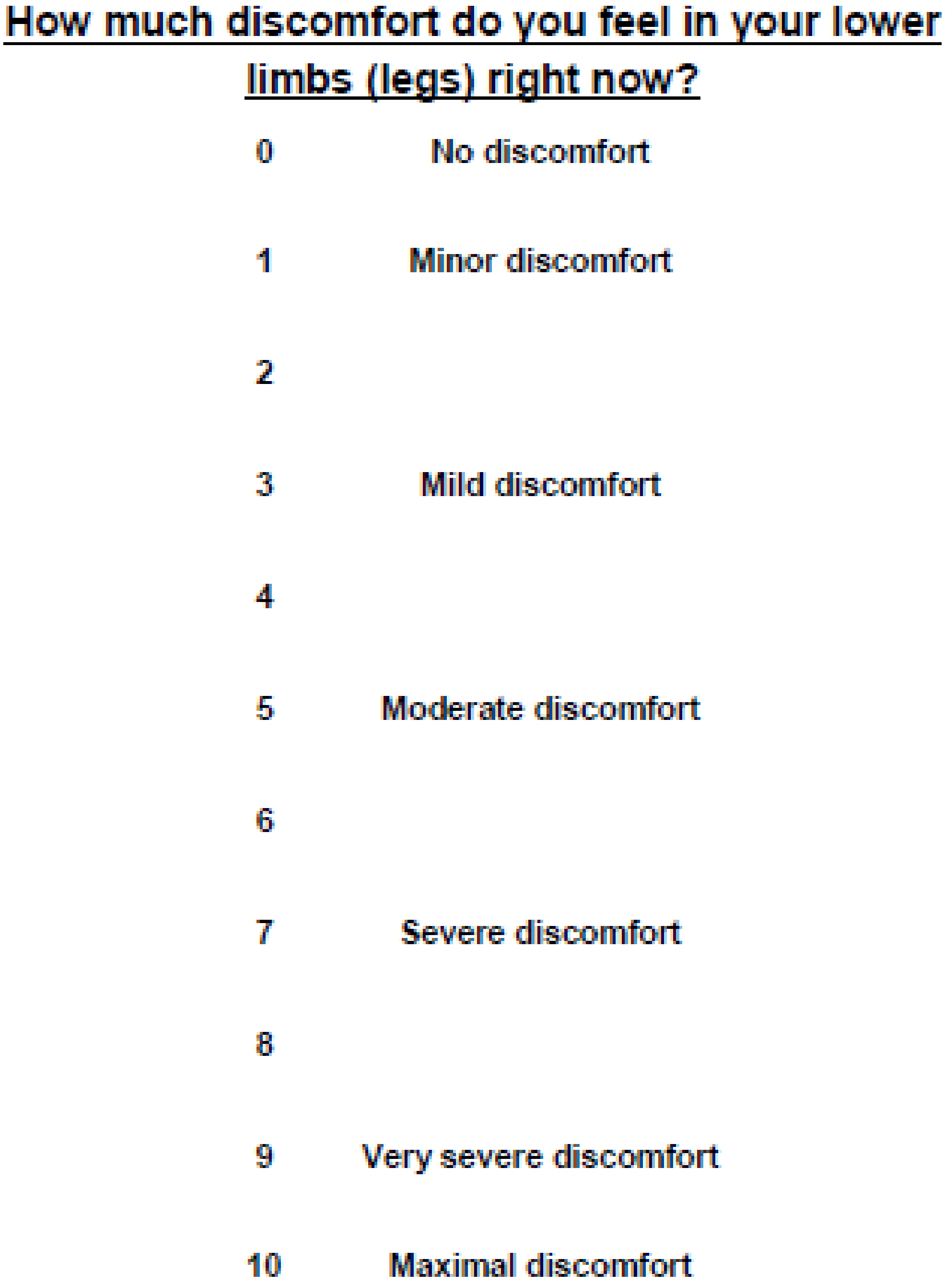
**Appendix 3** Perceived breathlessness scale (Ward & Whipp, 1989).



How difficult does it feel to breathe right now?

| | |
|---|---|
| 0 | Nothing at all |
| 0.5 | Very, very slight (just noticeable) |
| 1 | Very slight |
| 2 | Slight |
| 3 | Moderate |
| 4 | Somewhat severe |
| 5 | Severe |
| 6 | |
| 7 | Very severe |
| 8 | |
| 9 | Very, very severe (almost maximal) |
| 10 | Maximal |

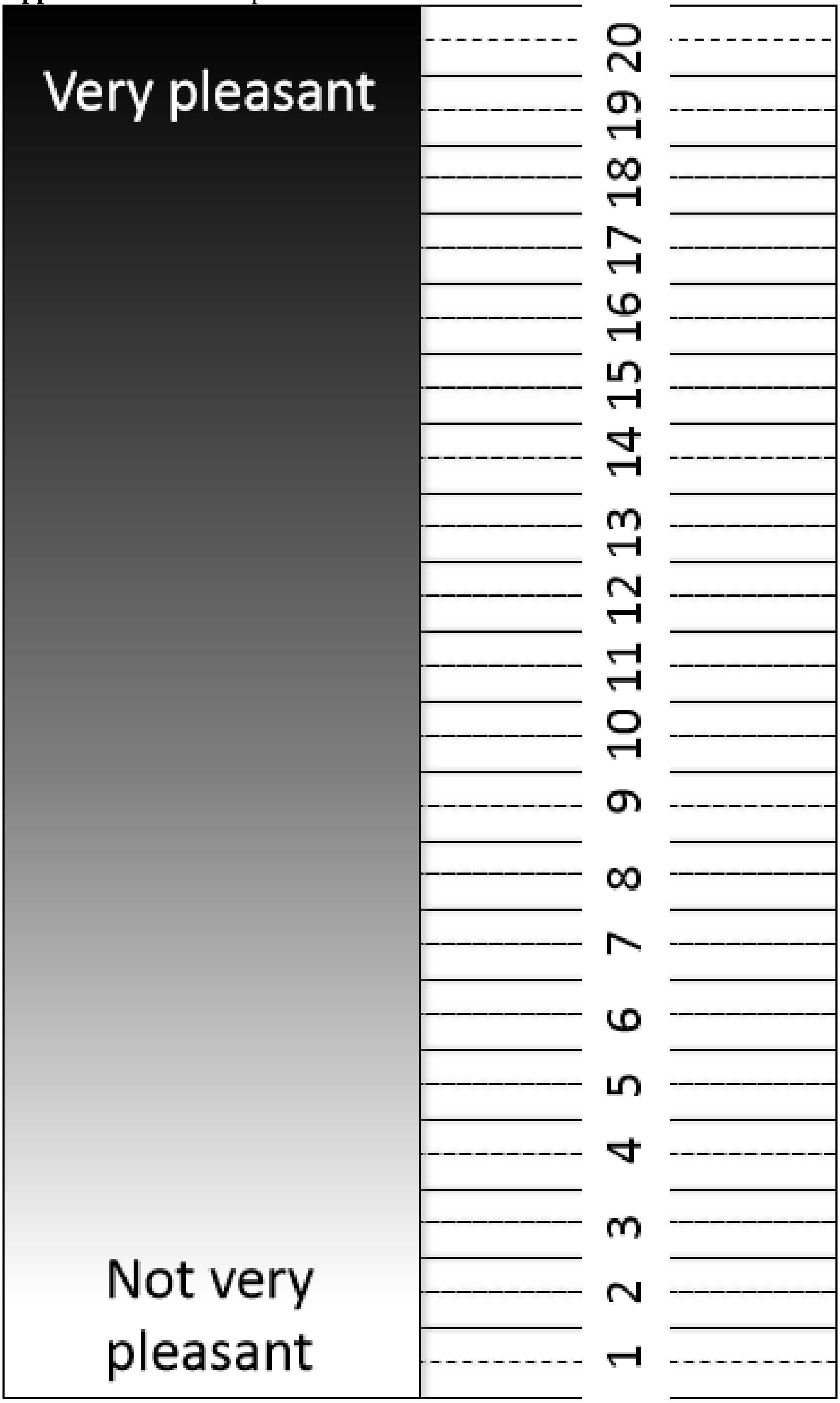
**Appendix 4** Perceived limb discomfort scale.



## How much discomfort do you feel in your lower limbs (legs) right now?

| | |
|---|---|
| 0 | No discomfort |
| 1 | Minor discomfort |
| 2 | |
| 3 | Mild discomfort |
| 4 | |
| 5 | Moderate discomfort |
| 6 | |
| 7 | Severe discomfort |
| 8 | |
| 9 | Very severe discomfort |
| 10 | Maximal discomfort |

**Appendix 5** Perceived pleasure scale.

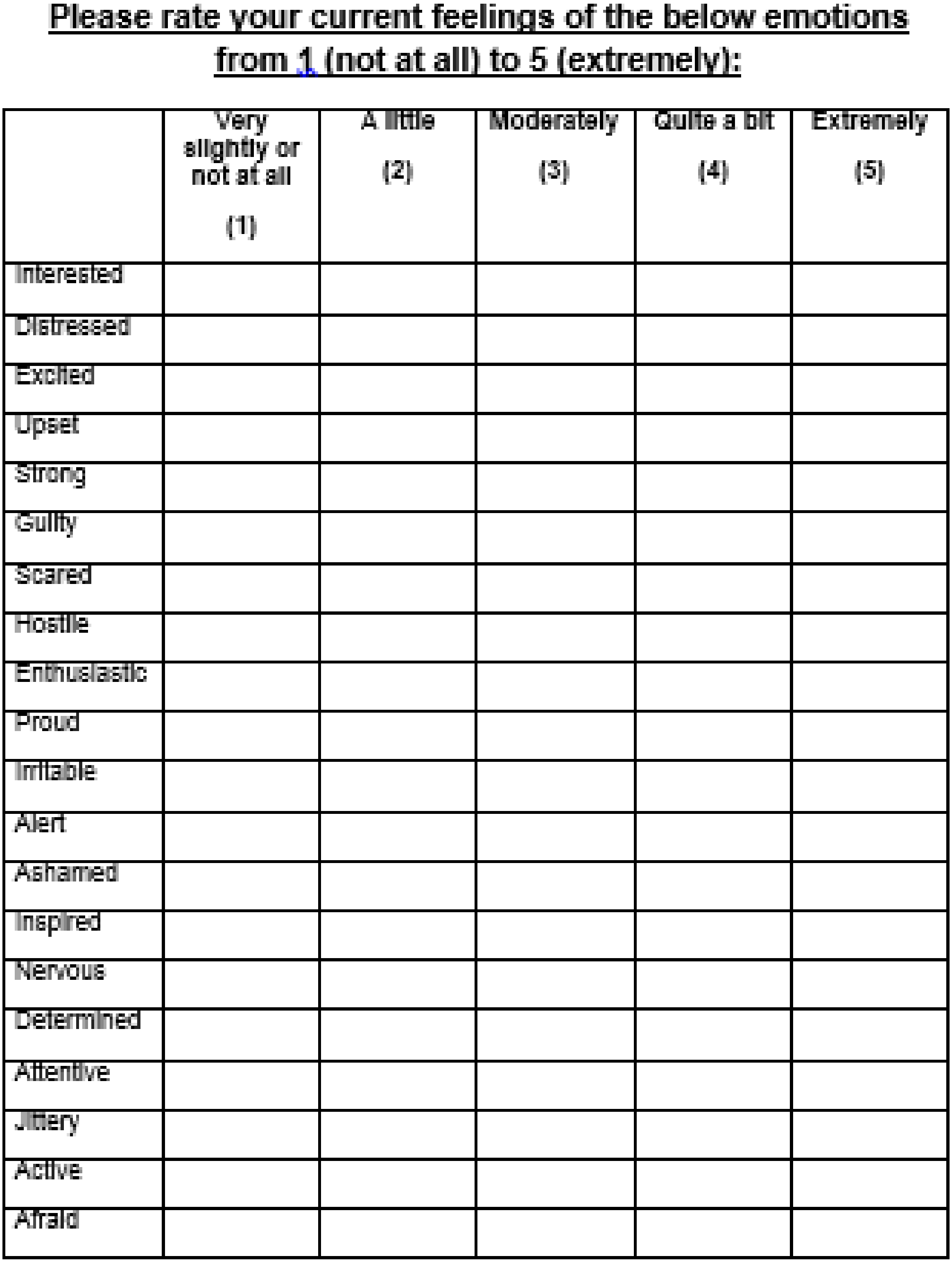


**Appendix 6** Perceived mood state scale (Hardy & Rejeski, 1989).

# How do you feel right now?

| | |
|---|---|
| +5 | Very good |
| +4 | |
| +3 | Good |
| +2 | |
| +1 | Fairly good |
| 0 | Neutral |
| -1 | Fairly bad |
| -2 | |
| -3 | Bad |
| -4 | |
| -5 | Very bad |

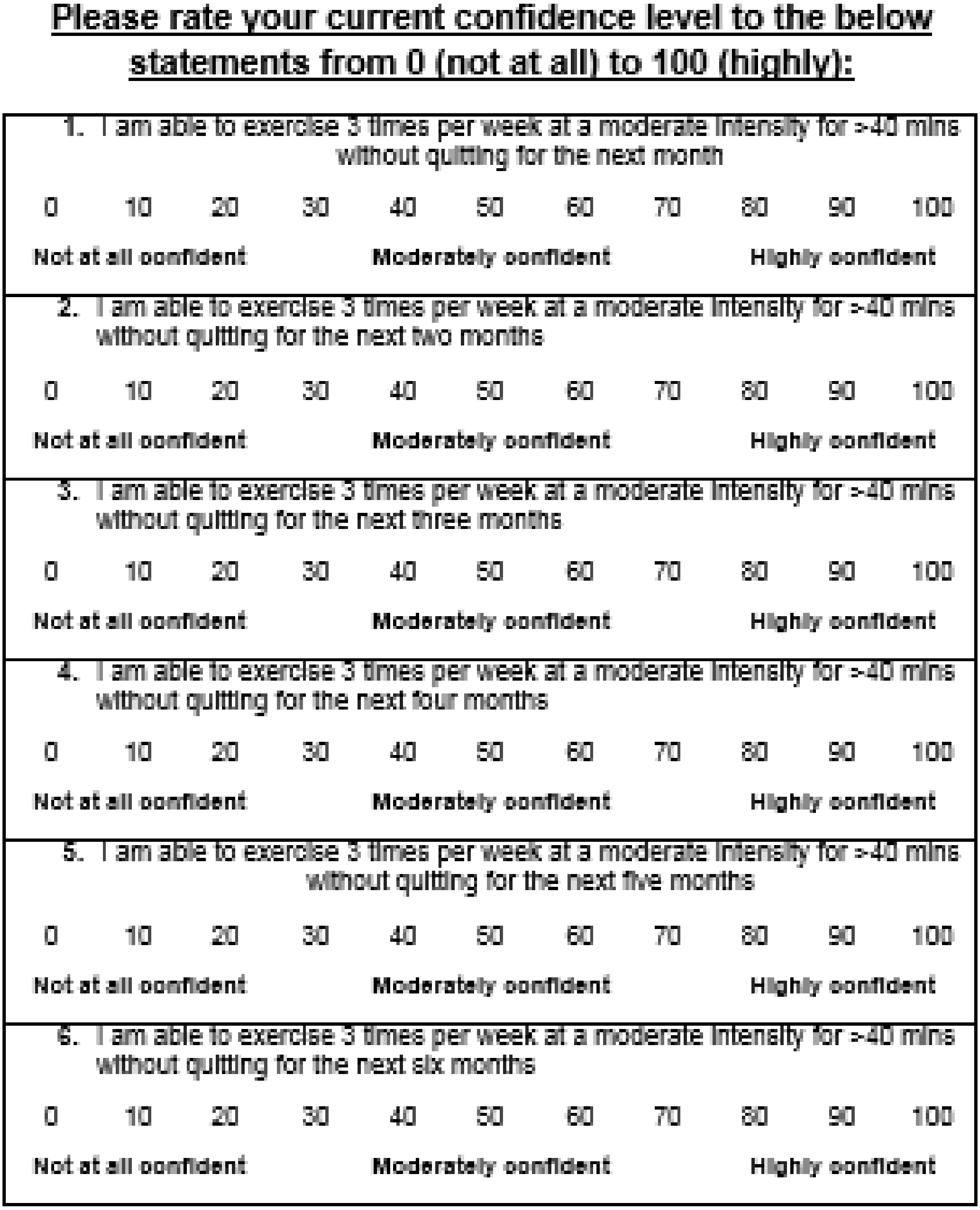
**Appendix 7** Positive and negative affects schedule scale (Watson & Clark, 1988).



**Please rate your current feelings of the below emotions from 1 (not at all) to 5 (extremely):**

| | Very slightly or not at all (1) | A little (2) | Moderately (3) | Quite a bit (4) | Extremely (5) |
|---|---|---|---|---|---|
| Interested | | | | | |
| Distressed | | | | | |
| Excited | | | | | |
| Upset | | | | | |
| Strong | | | | | |
| Guilty | | | | | |
| Scared | | | | | |
| Hostile | | | | | |
| Enthusiastic | | | | | |
| Proud | | | | | |
| Irritable | | | | | |
| Alert | | | | | |
| Ashamed | | | | | |
| Inspired | | | | | |
| Nervous | | | | | |
| Determined | | | | | |
| Attentive | | | | | |
| Jittery | | | | | |
| Active | | | | | |
| Afraid | | | | | |

**Appendix 8** Exercise-self efficacy scale (Smith et al., 2012).



**Please rate your current confidence level to the below statements from 0 (not at all) to 100 (highly):**

1. I am able to exercise 3 times per week at a moderate intensity for >40 mins without quitting for the next month

0 10 20 30 40 50 60 70 80 90 100

**Not at all confident** **Moderately confident** **Highly confident**

2. I am able to exercise 3 times per week at a moderate intensity for >40 mins without quitting for the next two months

0 10 20 30 40 50 60 70 80 90 100

**Not at all confident** **Moderately confident** **Highly confident**

3. I am able to exercise 3 times per week at a moderate intensity for >40 mins without quitting for the next three months

0 10 20 30 40 50 60 70 80 90 100

**Not at all confident** **Moderately confident** **Highly confident**

4. I am able to exercise 3 times per week at a moderate intensity for >40 mins without quitting for the next four months

0 10 20 30 40 50 60 70 80 90 100

**Not at all confident** **Moderately confident** **Highly confident**

5. I am able to exercise 3 times per week at a moderate intensity for >40 mins without quitting for the next five months

0 10 20 30 40 50 60 70 80 90 100

**Not at all confident** **Moderately confident** **Highly confident**

6. I am able to exercise 3 times per week at a moderate intensity for >40 mins without quitting for the next six months

0 10 20 30 40 50 60 70 80 90 100

**Not at all confident** **Moderately confident** **Highly confident**