A Randomized Trial of Exercise Training Versus Relaxation for the Treatment of Chronic Insomnia in Obstructive Sleep Apnea

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Abstract

Background:

Obstructive Sleep Apnea Syndrome (OSA) is a common sleep disorder characterized by partial or complete blockage of the pharyngeal airway during sleep, posing as a significant public health concern. OSA is often comorbid with chronic insomnia (COMISA). Insomnia disorder involves a difficulty initiating sleep, maintaining sleep and/or early awakenings, despite time and opportunity for sleep, causing impairments in daytime functioning and significant distress. Individuals with COMISA suffer from worse sleep and daytime functioning, compared to individuals presenting with either disorder in isolation. Due to their insomnia complaints, these individuals tend to be less compliant with continuous positive airway pressure (CPAP) therapy, the gold standard treatment for OSA. Cognitive behavioural therapy for insomnia (CBTi) has shown promising results in this population but can be difficult for individuals to access, and alone, cannot improve OSA severity. This unique group requires a therapy targeted to both disorders, which would potentially improve apnea-hypopnea index (AHI) and/or insomnia symptomology for a better sleep. Currently, no effective therapy tailored to these individuals has been found. Exercise is a potential non-pharmacological therapy that would simultaneously improve symptoms of both disorders. Studies examining the effects of exercise as a therapy for COMISA are lacking, and research examining exercise as a therapy for either of the two disorders alone yield mixed results likely due to variation in methodology and treatment approach.

Objectives:

(1) To determine if an 8-week exercise intervention would improve insomnia severity in patients with comorbid OSA and insomnia when compared to an 8-week active control condition of relaxation therapy. **(2)** To examine the effects of the exercise and relaxation interventions on cardiorespiratory fitness both within-groups and between-groups. **(3)** To examine if improvements in cardiorespiratory fitness would be associated with improved changes in objective and subjective sleep quality.

Methods:

Sixteen participants (10 female, 54.9 ± 13.4 years of age) were randomised to 3 weekly sessions of exercise training or self-guided relaxation. The exercise sessions consisted of 60 minutes of moderate-intensity aerobic and resistance exercise, with 1 weekly session supervised and the remaining two unsupervised at home or in the community. The protocol included a screening polysomnography (PSG) night, a cardiopulmonary exercise test, and an overnight PSG, as well as questionnaires (including the Insomnia Severity Index (ISI)) before and after the 8 weeks. All PSG recordings were sampled at 512 Hz (Somnomedics, Germany) and sleep stages were scored offline according to AASM guidelines. ISI and sleep efficiency (SE) (extracted from PSG) were assessed as primary outcomes. VO_{2peak} (ml/kg/min), VO_2 at the ventilatory threshold (VT), heart rate (HR) at 50% isotime (ISO) pre- and post- intervention were assessed as secondary outcomes. Bivariate correlations were also performed to examine any potential relationships between change in cardiorespiratory fitness and change in subjective and objective sleep parameters.

Results:

Results revealed a significant effect of time (pre, post 8-weeks) on ISI score ($F(1,14)= 12.315$; $p=.003$), but no significant effect of condition (exercise, relaxation) or time*condition interaction. Both exercise and relaxation had large effects on ISI, with exercise showing a larger effect size (Cohen's $d= 3.88$) than relaxation (Cohen's $d= 0.184$). No significant effects were found for SE. A significant time*condition interaction was found for VO_{2peak} (ml/kg/min) ($F(1,15)= 10.724$; $p=.006$), with the exercise condition showing improvements. Spearman correlations indicated a non-significant association for change in ISI and change in VO_{2peak} (ml/kg/min) ($r=0.59$; $p>.05$).

Conclusions:

Both exercise and relaxation reduced insomnia severity in people with COMISA, with exercise having a larger effect. Objective measures of sleep efficiency did not improve significantly in either group. Cardiorespiratory fitness improved with the partly home-based, moderate-intensity aerobic and resistance training intervention used in this study. Larger trials are warranted to confirm these findings.

Significance:

This is the first randomized controlled trial (RCT) to examine the effects of an exercise intervention on sleep in this specific COMISA population.

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1. Literature Review

1.1 Sleep

Sleep is a fundamental part of human health. Epidemiological and experimental studies indicate that getting enough sleep is associated with improved learning and memory, cellular repair, brain development, and metabolism. In contrast, sleep loss can impair endocrine and immune functions, and may put individuals at an increased risk of hypertension, obesity, and diabetes[1–11].

There are two main categories of sleep: rapid eye movement (REM), and non-rapid eye movement sleep (NREM), which can be further separated into three stages of sleep, each characterized by specific changes in EEG signals[12]: stage one (NREM1 or N1), stage two (N2), and stage three (N3). Stage N1, characterized by a decrease in alpha waves and increase in theta waves, usually occurs while falling asleep after wake and is considered light sleep. N2 generally occurs after N1, although this is not always the case, and is a period of sleep involved in memory consolidation, accounting for almost half of a healthy night of sleep. N2 is characterized by the appearance of sleep spindles and K-complexes. Stage N3 is a period of deep sleep, categorized in EEG by delta waves, during which an individual becomes less responsive to external stimuli. Lastly, REM sleep is the period of sleep in which vivid dreams occur. During REM sleep, heart rate and breathing may increase, and skeletal muscles are temporarily paralyzed, except for the eyes, leading to rapid ocular movements.

Sleep can be measured objectively using polysomnography. Polysomnography (PSG) is a combined measure of electroencephalogram (EEG) to measure electrical activity in the brain, electromyogram (EMG) to measure muscle movement, electrooculogram (EOG) to measure eye movement, electrocardiogram (ECG) to measure cardiovascular activity. PSG also includes

additional physiological measurements to measure respiratory function (through thoracic and abdominal movement and nasal-oral thermocouple airflow), snoring (with a snore sensor), and SpO_2 (with a pulse oximeter). Polysomnography is the gold-standard method for measuring sleep architecture.

Once PSG data is obtained and sleep stages are scored based on the EEG signal, in accordance to AASM scoring rules[12], several important variables on the sleep macroarchitecture can be extracted, including but not limited to: total sleep time (TST) (i.e. The total amount of time spent sleeping), wake after sleep onset (WASO) (i.e. The amount of time spent awake after sleep has been initiated), sleep onset latency (SOL) (i.e. The time it takes to fall asleep once in bed with the lights out), sleep efficiency (SE) (i.e. The time spent asleep divided by the total amount of time in bed), the percent of time spent in each sleep stage, sleep fragmentation index (SFI) (i.e. total number awakenings and shifts to stage 1 divided by TST), and arousals (i.e. periods of sudden increase in frequency in the EEG, denoting cortical activation). These variables are commonly used to quantify different aspects of sleep quality and are useful when examining sleep patterns in healthy sleepers and individuals with sleep disorders.

1.2 Obstructive Sleep Apnea (OSA)

Obstructive Sleep Apnea (OSA) is a common breathing-related sleep disorder caused by narrowing or obstruction of the pharyngeal airway during sleep, which impairs breathing and airflow. According to the most recent Canadian Health Measures Survey (CHMS) in 2016 and 2017, 6.4% of Canadians reported being diagnosed by a professional with sleep apnea; although they do not make the distinction between central or obstructive sleep apnea[13]. Globally, prevalence is estimated to be around 1 billion people worldwide suffering from OSA, and this is thought to

be increasing due to rising obesity rates and aging[14]. Risk factors linked to OSA include: older age, excess body weight, a larger neck circumference, sedentary lifestyle, smoking, alcohol consumption, nasal congestion, and hormonal changes during menopause [15,16].

OSA can be diagnosed in a sleep clinic using PSG. Severity of OSA is calculated by the number of apneas and hypopneas per hour, the apnea-hypopnea index (AHI). An apnea is defined as the total cessation of airflow for at least ten seconds, denoted by a drop in peak signal excursion ≥ 90% of oronasal thermal signal or pressure signal. This can be witnessed in-lab using an oronasal flow sensor. A hypopnea is a decrease in airflow for at least ten seconds, denoted by a ≥ 30% drop in peak signal excursion from pre-event baseline and combined with either a drop ≥ 3% in arterial oxygen desaturation or an arousal. OSA disorder is defined as an AHI of 5 or more[17]; with 5-15 being mild, 15-30 being moderate, and above 30 being severe. As a result of apnea and hypopnea events, individuals with OSA may experience microarousals or prolonged arousals throughout the night. While some people with OSA wake during the night gasping for air, many are unaware of their arousals. Consequently, many individuals may suffer from diurnal symptoms associated with OSA without understanding the cause. Symptoms of OSA include: snoring, excessive daytime sleepiness, fatigue, non-refreshing sleep, nocturia, morning headache, irritability, memory loss, impaired cognitive functioning, and decreased quality of life[18,19]. While several symptoms of OSA are shared in individuals with Central Sleep Apnea, it is important to differentiate between these two disorders. Central Sleep Apnea involves impaired signalling from the brain to the muscles involved in respiration during sleep; whereas, in OSA brain signalling for breathing is intact, but airflow is blocked or narrowed physically.

A variety of factors have been found to contribute to OSA pathogenesis. These include a narrow, crowded or collapsible upper airway, dysfunction of the pharyngeal dilator muscle during

sleep, a lower threshold for arousal from airway narrowing, and unstable control of breathing[18]. A narrow upper airway can be due to a variety of factors, including physical causes, such as a larger tongue or idiopathic narrow upper airway. Obesity can also contribute to a narrow upper airway, via adipose tissue deposition surrounding the airway (within the neck and pharyngeal muscles), and within the tongue[20]. Additionally, individuals with obesity may have adipose tissue surrounding the abdomen, thereby reducing lung capacity, which can increase collapsibility of the upper airway[20]. Patients may be at increased risk for OSA due to one or a combination of these factors.

1.3 Insomnia

Insomnia involves difficulty initiating sleep onset, maintaining sleep and/or early awakenings that persist despite adequate time and opportunity for sleep, causing clinically significant distress and daytime functioning impairments. For a diagnosis of chronic insomnia disorder, these complaints of sleep disturbances and daytime impairments must occur 3 or more times a week for over 3 months. If symptoms have persisted for less than 3 months, acute insomnia can be diagnosed[21,22]. Numerous health risks have been linked to insomnia, including but not limited to: cardiovascular disorders[23], increased mortality risk[23–25], hypertension, psychiatric disorders[26–28], and problems in the workplace leading to indirect costs of around $28 billion in 2005[29].

Insomnia disorder has become an increasing problem in Canada. Prevalence values vary, depending on classification methods used to assess insomnia disorder[21]. It is important to differentiate insomnia symptoms from insomnia disorder. While insomnia symptoms are transient, insomnia disorder is chronic, persisting for at least three months. Insomnia disorder is estimated to affect 9-10% of adults in the general population, according to a study of individuals in Quebec,

Canada[30]. However, more recently, Health Statistics Canada has reported a 23.8% prevalence of insomnia symptoms in Canadians[31]. An estimated 25-30% of adults may show symptoms of insomnia without meeting all criteria for and insomnia disorder diagnosis[30,32,33]. Certain populations are more likely to experience insomnia. Symptoms are more prevalent among women[21,31], older individuals[21], individuals with lower socio-economic status[31], and individuals reporting a medical condition and poor quality of life[31].

Currently, there is no single accepted theory for the etiology of insomnia. Phenotypes of insomnia are heterogenous, with individuals presenting with various symptoms and comorbidities. Several potential pathophysiological models have been proposed, including: general hyperarousal, genetic, molecular, and cellular mechanisms, along with the dysregulation of sleep-wake brain networks[21,34,35]. Psychological models include: faulty conditioning, dysfunctional thinking, paradox and ironic control[36]. A common theory suggests that hyperarousal before bedtime and during sleep may contribute to insomnia symptoms, making it more difficult to fall and remain asleep. Hyperarousal can be described as increased physiological, cortical, and cognitive activation, as well as emotional arousal that can interfere with disengagement from the environment and sleep[34]. Hyperarousal can be witnessed in the EEG as a sudden increase in signal frequency, and has been observed in individuals with primary insomnia[37–39].

Insomnia severity is commonly examined using self-report questionnaires, such as the Insomnia Severity Index (ISI) and the Pittsburgh Sleep Quality Index (PSQI). It can also be examined with objective PSG recordings to examine variables such as SOL, TST, WASO, and SE. For example, a difficulty falling asleep for someone suffering from insomnia could present as an increased SOL in a PSG, or difficulty maintaining sleep could be represented by an increased WASO, both leading to decreased SE.

1.4 Comorbid Insomnia and Obstructive Sleep Apnea (COMISA)

About 39 to 58% of patients with OSA have comorbid primary insomnia[40]. The combination of Obstructive Sleep Apnea and Insomnia (COMISA) can be particularly troublesome. In addition to initial insomnia symptomology, patients with COMISA may wake up throughout the night due to the obstruction of airflow, but rather than falling back asleep, may be unable to resume sleep again due to their insomnia disturbances. These individuals report more severe sleep disturbances than those with either disorder alone[41]. This group experiences worse daytime functioning, lower quality of life, and higher rates of cardiovascular disease and depression than those with only one of the disorders[42,43]. It has also been found that those with both disorders spend less time in deep sleep and have more sleep fragmentation than those with insomnia alone[41].

The diagnosis of COMISA can be difficult. The two disorders share many overlapping symptoms[40,44]. Some shared symptoms include: frequent awakenings, difficulty falling asleep, unrefreshing sleep, fatigue, daytime sleepiness, impairments in attention, cognition and memory, social and occupational dysfunction, mood disturbances, reduced motivation and energy, increased risk for accidents, feelings of worry about sleep, and decreased quality of life[40]. In a research context, studies examining participants with COMISA have used various methods of diagnosis. Diagnosis is best conducted using a combination of PSG, to confirm AHI, and subjective measurements, such as questionnaires, to gauge insomnia symptoms attributable to post-apneic nocturnal awakenings. Some studies have searched for OSA in individuals with insomnia, some have tried diagnosing insomnia in individuals with OSA, and some have tried simultaneously diagnosing both disorders[44].

1.5. Current Treatments

1.5.1 Current Treatments for OSA

Continuous Positive Airway Pressure (CPAP)

The gold-standard treatment for OSA is continuous positive airway pressure (CPAP) ventilation. CPAP has been shown to improve AHI[45], normalize sleep architecture, elevate mood, improve daytime functioning and reduce sleepiness, reduce automobile accidents and decrease risk of cardiovascular events in patients with OSA[19,46]. When compared to all of the current minimally invasive treatments for OSA, CPAP was found to be the most effective in AHI reduction[45]. CPAP has also been found to increase time in deep sleep stages (N3) and reduce EEG arousals[19]. Despite these documented benefits, CPAP may lack therapeutic potential due to poor compliance. Patients often stop using the CPAP, or take it off during the night due to nasal discomfort, mask leaks, congestion and claustrophobia[47]. Use of the CPAP for 6 or more hours during the night has been shown to improve daytime sleepiness and functioning and to restore memory. However, 43-86% of OSA patients adhere to less than four hours during the night[46]. Some of these individuals who do not adhere to the CPAP have comorbid insomnia, which is a risk factor for poor compliance to CPAP[46,48]. In a longitudinal cohort study by Björnsdóttir et al., COMISA patients using CPAP consistently for two years showed an improvement in insomnia symptoms involving sleep maintenance; however, sleep initiation and early morning awakenings persisted despite CPAP use.[48] Insomnia could also be developed as a consequence of using the CPAP. A therapy for OSA which is equally effective as CPAP, but more practical and easier to adhere to is desirable.

Lifestyle Modifications

Since obesity is a risk factor for OSA, with 70% of OSA patients classified as obese[49], several lifestyle modifications targeting weight-loss with methods such as diet and exercise have been

examined to improve OSA symptomology. Lifestyle modification methods previously examined include: diet instruction[50–52], very low-calorie diets[52–54], behavioural therapy for eating habits[52,55], and exercise[52]. Other therapies for OSA include: a cervico mandibular support collar, mandibular advancement device, myofunctional therapy, oral negative pressure therapy, positional therapy, and a tongue stabilizing device[45]. However, when comparing these devices to CPAP and exercise, CPAP was found to be the most effective at improving AHI, and exercise was the most effective at improving scores on the Epworth Sleepiness Scale (ESS)[45], a validated measure of daytime sleepiness.

1.5.2 Current Treatments for Insomnia

Pharmacotherapy

The primary pharmacological treatments for insomnia are those with a sedative effect such as gamma-aminobutyric acid receptor agonists like benzodiazepines and z-hypnotics. These drugs can shorten SOL, increase TST, and time spent in NREM[56]. However, these medications have been shown to decrease time spent in slow wave sleep (stages three and four) for a less restorative night of sleep, and are met with several undesirable side effects, including but not limited to depression and anxiety, cognitive deficits, and an increased risk of falls[57–61]. GABAα- agonist drugs are best when used in a short-term period, for four to six weeks. Long-term use of pharmacotherapy has not been proven to be effective, as the drugs may result in tolerance, dependence, and rebound insomnia when drug-use is stopped[62].These drugs are generally not recommended for individuals with COMISA, as research suggests that they may prolong apnea or hypopnea events[63]

Cognitive Behavioural Therapy for Insomnia (CBTi)

Cognitive behavioural therapy for insomnia (CBTi) has been recognized as an effective treatment option and is the first line of treatment for insomnia, with a treatment response rate of 60% and total remission rate after two years of 40%[64]. CBTi is a multimodal sleep-focused intervention conducted by a psychologist, and usually lasts over 6-8 weeks. CBTi components include teaching sleep hygiene, stimulus control, sleep restriction therapy, cognitive restructuring, and relaxation methods[29,65]. In a meta-analysis comparing CBTi to pharmacotherapy, CBTi was shown to be equally effective in the short-term for improving number of awakenings, wake time after sleep onset, total sleep time, and sleep quality, and was shown to be more effective for sleep onset latency[62]. CBTi has been shown to be more successful than drug therapy for long-term treatment of insomnia[65]. While CBTi is the current first-line treatment for insomnia, still, 40% of patients do not respond to treatment[30].

Relaxation Therapy

Relaxation interventions are based on the premise that individuals with insomnia have elevated levels of arousal around bedtime[66]. There are two main types of relaxation therapy; those intended to reduce somatic tension and those intended to lower cognitive arousal and intrusive thoughts before sleep[66,67]. Relaxation therapies to reduce somatic tension may include diaphragmatic breathing exercises, or controlled deep breathing, and progressive muscle relaxation, a method involving the controlled tension and relaxation of various groups of muscles throughout the body. Additionally, guided imagery is a visualization technique which can be used to reduce intrusive thoughts or cognitive arousal before sleep. According to a 1999 review by Morin et al., there is a medium effect size of relaxation therapy on the number of awakenings (d=0.37-0.57) and total sleep time (d=0.53-0.57) in individuals with insomnia[66]. A more recent systematic review by

Edinger et al., recommends relaxation therapy as a conditional recommendation for chronic insomnia treatment, suggesting that most patients should receive relaxation therapy as a single-component therapy, with different choices appropriate for different patients[68].

1.5.3 Treatment for COMISA

Treatment for COMISA can be particularly challenging. Benzodiazepines are the most commonly used drug for insomnia, but are not recommended for long-term treatment for sleep apnea patients as they can be associated with decreased upper airway muscle tone and ventilatory response to hypoxia[42,69]. This could lead to longer apneas and hypopneas, which could cause more harm. The most effective treatment approach for this group is still unclear. As mentioned previously, the gold-standard treatment for OSA is CPAP therapy. It has been found that in participants presenting with both disorders, there is a reduced acceptance and adherence to CPAP[44,70]**.** Since CPAP cannot help to improve insomnia and CBTi alone cannot improve the physiological causes of OSA, one solution may be to combine CBTi prior to CPAP in COMISA patients to improve adherence. Recently, Sweetman et al. found that effectiveness of CBTi was no different in those with COMISA vs. insomnia alone[71]. Improving insomnia symptoms with CBTi may increase the effectiveness of CPAP for this population. The problem with CBTi is that it is costly, time consuming, and difficult to access. Also, CBTi alone cannot improve AHI. It must be combined with CPAP treatment to target OSA, and not all individuals wish to use the CPAP machine. A more-practical solution for patients suffering with COMISA would be helpful, and one that could target insomnia symptomology and AHI alone, without the use of a CPAP would be optimal; however, more research on therapies for this specific group needs to be done.

1.6 Exercise

Physical activity is defined by the World Health Organization as "any bodily movement produced by the skeletal muscles that results in energy expenditure."[72] Although often used interchangeably, the term "exercise" refers to a subset of physical activity which is planned, structured, and repetitive and has an objective of maintaining or improving physical fitness[72]. According to the Canadian Society for Exercise Physiology, moderate- vigorous intensity exercise for 150 minutes per week can help reduce the risk of: premature death, heart disease, stroke, high BP, certain types of cancer, type two diabetes, osteoporosis, and obesity[73]. It can also improve fitness, strength and mental health[73]. Additionally, exercise has shown promising positive effects on sleep[57,74,75], which could make it a non-invasive, cost-effective solution, with positive side-effects, for those suffering from comorbid OSA and insomnia.

1.6.1 Potential Mechanisms

The exact mechanism linking physical activity to sleep quality in healthy sleepers, individuals with insomnia, and those with OSA is not yet fully understood. However, theories examining the effects of exercise on thermoregulation, autonomic function, immune function, and mood, which subsequently affect sleep have been proposed and examined, along with theories involving weight-loss, upper airway muscle tonus, and alterations in control of breathing for those with OSA.

It has been suggested, and evidence supports, that increases in body temperature following an acute exercise session can elicit a homeostatic process which drives peripheral heat loss, via methods such as vasodilation, resulting in a rapid decline in core temperature, which stimulates

sleep onset and increases slow wave sleep[76,77]. This would not explain a chronic or long-term effect of exercise on sleep, but an acute effect.

Another mechanism which may contribute to a positive effect of acute exercise on sleep involves autonomic function. Autonomic function is closely intertwined with sleep and exercise, with parasympathetic activity increasing during sleep and sympathetic activity decreasing[78]. During exercise, sympathetic activity increases and has been shown to improve vagal modulation[79]. Improved vagal modulation may be indicative of improved control of the parasympathetic system, which in turn could improve sleep[80].

When it comes to an effect of exercise on sleep, immune function may play a role. Immune function has a circadian response, with an increase in production of pro-inflammatory cytokines such as IL-2, IL-6, IL-12, TNF-α and IFN-γ, during sleep, and an increase in production of immune cells and anti-inflammatory cytokines, like IL-10, being produced during wakeful hours[76,81]. Disturbances in sleep have been shown to be associated with dysregulated immune function and low-grade systemic inflammation[82,83]. Both acute and chronic exercise modulate inflammatory markers. An acute exercise bout can affect immune parameters, with IL-6 being produced by skeletal muscles upon contraction[84], and leukocyte subsets along with plasma CRP and TNF-α, IL-1, IL-1ra, IL-10, and sTNF-r increasing[85]. Contrary to this acute effect, chronic exercise has shown to reduce resting levels of markers of inflammation; thereby being recommended as an anti-inflammatory therapy for systemic low-grade inflammation[84–86]. Cross-sectional observation studies examining the effects of chronic exercise on systemic markers of inflammation have found decreases in C-reactive protein (CRP), IL-6, and TNF-α with increased physical activity[87]. While sleep is closely linked to the immune system, and chronic exercise has shown anti-inflammatory

effects, more research needs to be done to determine if the anti-inflammatory effects of exercise modulate sleep.

Since insomnia is associated with increased anxiety and depression, one theory explaining the positive effect of exercise on insomnia involves its impact on mood. There is a bidirectional relationship between psychological distress and sleep[88,89]. Improving anxiety symptoms may improve sleep quality and lessen the time it takes to fall asleep for those with insomnia. Acute and long-term exercise has been shown to improve symptoms of anxiety and depression[90].

When it comes to the effect of exercise on OSA, weight-loss is an important variable to take into consideration. A higher BMI is a risk factor for OSA and for the development of sleep-disordered breathing[91]. Weight gain has been associated with increased AHI[92], but when it comes to the effects of weight-loss on AHI, results are mixed. Several weight-loss interventions have found a decrease in AHI in combination with a decrease in BMI[93–95]. Additionally, studies have found a decrease in AHI post-gastrectomy, supporting the hypothesis of weight-loss as a mediator of the effect of exercise on AHI[96,97]. However, some RCTs examining exercise interventions for individuals with OSA have found reductions in AHI post-intervention, without reductions in BMI[98–101]. This would suggest that exercise improves OSA severity, not only by contributing to weight loss, as measured by BMI, but through an independent role. One possibility involves exercise reducing subcutaneous fat surrounding the airway, thereby affecting its collapsibility, without influencing BMI. Whether or not improvements in OSA severity are associated with BMI or anthropometric measures is inconsistent[96–101].

1.6.2 Exercise Modality

When developing an exercise intervention for individuals with COMISA, several aspects of the exercise modality are important to take into consideration, such as: the timing, type, intensity, and dose of exercise. See Table 1 for an overview of these design features in several previous RCTs and interventions, and their corresponding main results. A large variety of exercise types have been utilized in exercise-intervention studies, including, but not limited to: karate, resistance training, step aerobics, walking, stationary cycling, yoga, Tai Chi, and tango dancing (See Table 1); however, no single type has been proven more efficacious at improving sleep. For exercise intensity, evidence of greater improvements in subjective sleep quality with higher resistance exercise intensity training has been observed[102]. Several aerobic exercise interventions use a light to moderate training intensity of 60-80% peak heart rate (See Table 1). An ideal exercise-training dose for various sleep improvements has not been quantified, as the number and duration of weekly sessions and the length of interventions vary greatly. Exercise session duration generally ranges from 30 minutes to 3 hours, with most RCTs using exercise bouts of 45-60 minutes (See Table 1). The exercise frequency used in previous RCTs ranges from once a week to six times a week, and the length of interventions vary from two weeks[103] to 12 months[104]. Regarding the timing of exercise, older sleep hygiene tips recommended not exercising before bedtime, but more recent studies using actigraphy and questionnaires suggest that exercise close to bedtime does not disturb sleep as long as it does not interfere with sleep time[76,90,105,106].

1.6.3 Exercise for Good Sleepers

Studies have looked at the effects of exercise interventions on sleep in different populations such as, good sleepers, individuals with insomnia, and individuals with sleep apnea. Studies support the fact that exercise does have an impact on sleep in regular, healthy sleepers; however,

due to a variety of intervention frameworks, exercise modalities, and variables measured, the exact effect of exercise on sleep has yielded diverse results. In a 1996 review of both cross-sectional and prospective studies, Kubitz et al. found that, in good sleepers, regular (chronic) exercise was associated with increases in slow wave sleep and total sleep time, and with decreases in REM sleep time, sleep onset latency, and time awake[74]. Several randomized controlled trials on individuals without sleep disorders have found significant improvements with exercise in subjective measures of sleep, most commonly in the validated Pittsburgh Sleep Quality Index (PSQI) questionnaire[57,75,102,104,107–112](See Table 1). Global PSQI scores, and PSQI subscales of SOL, TST, sleep efficiency, sleep quality, sleep dysfunction, and sleep disturbances have shown to improve in exercise based RCTs on good sleepers (See Table 1).

In good sleepers, evidence suggests an effect of physical activity on sleep quality; however, exercise interventions and measurements of sleep quality differ between studies. In addition, it is important to note that exploring the effects of exercise in healthy sleepers may underestimate its effects on sleep, due to a ceiling effect. Individuals with healthy sleep at baseline may not have as much room for improvement in sleep with exercise. Those with worse sleep at baseline have a greater potential to improve their sleep and have shown a greater response to sleep interventions[110]. It is crucial to examine exercise interventions on individuals with sleep disorders such as insomnia and OSA, because they may respond differently.

1.6.4 Exercise for Sleep Apnea

Numerous studies have examined the effects of both aerobic and resistance exercise on OSA, and overall, suggest a positive effect. A population-based longitudinal epidemiological study in 2012 by Awad et al., found an inverse association between self-reported hours of weekly

exercise and sleep-disordered breathing, even after adjusting for BMI[91]. A controlled case-series study by Cavagnolli et al., examined non-obese and sedentary male individuals with OSA and with no sleep disorder (as a control) and administered 24, 40-minute sessions of aerobic exercise (three sessions per week for 8 weeks), finding improved AHI in 80% of OSA patients following aerobic training, decreasing OSA severity in some[113].

Several RCTs have used PSG to measure the effects of exercise interventions in individuals with sleep apnea (See Table 1). A pattern emerging amongst these RCTs involves a decrease in AHI following an exercise intervention[93,99–101,114–116]. Contrary to this, an RCT by Roche et al., found no significant change in AHI in adolescents with severe obesity and OSA after a 9-month weight reduction program including interval training and moderate-high intensity activities[117]. Another conflicting RCT, by Torres-Castro et al., found no significant change in AHI in patients with moderate-severe OSA after an 8-week comprehensive community program including walking exercises. However, when only participants under the age of 60 were considered for analysis, a significant reduction in AHI was found[118]. Overall, exercise appears to improve AHI, but more studies need to be conducted. Three of the RCTs that examined a decrease in AHI post-intervention also reported a significant decrease in oxygen desaturation index (ODI) post-intervention[93,99,101], suggesting an improvement in OSA. Other sleep variables that have been observed with PSG to improve in individuals with OSA in RCTs post-intervention include: SWS[101], number of arousals[93,101], SE[114], and TST[117]; however, these have not been consistent throughout the literature.

RCTs have also examined subjective quality of sleep and daytime fatigue following an exercise intervention, using the PSQI[93,99] and ESS[93,100,118] (See Table 1). No changes in ESS following an exercise-based intervention were found, but of the studies examining PSQI scores, both found significant decreases in the global PSQI score post-trial[93,99].

Overall, previous research suggests that exercise training may improve objectively measured AHI in individuals with OSA. The effects of exercise training on subjective measures and on other PSG sleep variables remain inconclusive.

1.6.5 Exercise for Insomnia

Physical activity has been positively associated with sleep outcomes in people with sleep disruptions at baseline. In a cross-sectional study of 463 subjects with sleep disturbances, physical fitness was shown to be associated with a reduced risk of insomnia, with women in the upper tertile of physical fitness and upper body strength at a 92% and 76.4% decreased risk of sleep disturbances, assessed with the Jenkins Sleep Scale, compared to the lower tertile, respectively[119]. Consistent with this study, a 10 year-long longitudinal study of 5062 participants found a protective effect of high levels of physical activity on future risk for insomnia[120]. In addition, sedentary individuals with self-reported sleep problems report less-high intensity physical activity, after adjusting for potential confounders[121].

RCTs examining exercise as a therapy for insomnia have used a variety of methodology and have obtained conflicting results (See Table 1). Some patterns that have emerged from the literature include: improved PSQI scores[122–125], decreased sleep onset latency (SOL) measured with PSG[82,123] and PSQI[82,125], and increased sleep efficiency (SE), measured by actigraphy[124], PSG[82,123], and PSQI[125], following an exercise intervention. A study by Passos et al., examining the effects of a long-term moderate aerobic exercise intervention, consisting of 50 minute treadmill sessions 3 days per week for 6 months on SOL, WASO, and SE (all extracted from PSG) in individuals with chronic primary insomnia, found large effects of the training on all three parameters (d= -0.96; d=-1.66; d=1.91; respectively)[123]. Overall, PSG results for variables

indicative of insomnia severity are mixed, with some RCTs finding no significant between-group changes in PSG variables post-intervention[122,124,126]. A wide variety of exercise modalities, along with different classification methods for insomnia, and different outcome measures may be contributing to these diverging results.

2. Rationale

While studies have found significant effects of physical activity on insomnia and OSA individually, to our knowledge, no study has looked at the effects of exercise on a specific group of individuals with both disorders combined. Considering the fact that almost half of individuals with OSA have comorbid insomnia, and that a combination of the two disorders lessens the efficacy of the CPAP due to worse compliance, therapeutic studies in people with COMISA are much needed. Since CPAP therapy will not improve insomnia symptomology, and CBTi may improve compliance to the CPAP, but will not improve apneas or hypopneas on its own, a new therapy is warranted. Exercise training has shown promising results in improving characteristics of insomnia and OSA and may be an alternative method for patients suffering from both diseases. The goal of this study was to examine whether an eight-week intervention of moderate-intensity aerobic exercise combined with individualized resistance training would improve insomnia symptomology and sleep efficiency in individuals with COMISA in comparison to a control intervention of relaxation therapy alone.

3. Objectives

3.1 Primary Objective

The primary objective of this thesis was to determine if an 8-week exercise intervention improved insomnia severity in patients with COMISA, compared to an 8-week active control condition of relaxation therapy. Insomnia severity was measured using the validated self-reported Insomnia Severity Index (ISI) questionnaire, in combination with an objective measure of sleep efficiency assessed using PSG.

3.2 Secondary Objective

The secondary objective was to examine changes in cardiorespiratory fitness with the intervention, both within-groups and between-groups. Cardiorespiratory fitness was determined by VO_2 peak mainly, as well as VO_2 at the ventilatory threshold (VT), and heart rate (HR) at 50% ISO time.

3.3 Tertiary Objective

The final objective was to examine if improvements in cardiorespiratory fitness, with the 8-week exercise intervention, would be associated with changes in subjective insomnia severity.

4. Hypotheses

4.1 Primary Hypothesis

A reduction in insomnia symptomology, represented by scores from the ISI and by PSG scores of sleep efficiency, was expected in both groups, with a greater reduction in the exercise group.

4.2 Secondary Hypothesis

Measures of cardiorespiratory fitness were expected to significantly improve in the exercise group but not the relaxation group.

4.3 Tertiary Hypothesis

A significant negative correlation was expected between change in cardiorespiratory fitness and change in ISI score within the group receiving the exercise intervention.

5. Methods

5.1 Study Design

This thesis project was part of a larger pilot study, consisting of a 16-week intervention, with pre-, mid- (at 8 weeks), and post-intervention exercise testing and sleep recording measurements. The larger study is examining the effects of CBTi and exercise combined, in comparison to an exercise-only control group, on the severity of COMISA. See Figure 1 for the experimental design of the entire study.

This thesis project focused on the first 8 weeks of this study; comparing exercise training to a relaxation control condition (See red box in Figure 1). The experimental design for the first 8 weeks of this study is as follows. Participants first underwent screening using structured clinical interviews and PSG. Once eligibility was confirmed, they were be assigned a confidential participant number. Participants then took a pre-intervention symptom limited cardiopulmonary fitness test and stayed one night in the Sleep Lab at Concordia University's PERFORM Centre Sleep Laboratory for an EEG night. Once the pre-treatment assessment was completed,

participants were randomised to either an exercise group or relaxation group. Randomization was be conducted by block of four to ensure equal groups. Participants underwent either exercise training or relaxation for 8 weeks. At the end of the 8 weeks, the same cardiorespiratory and sleep assessments were conducted.

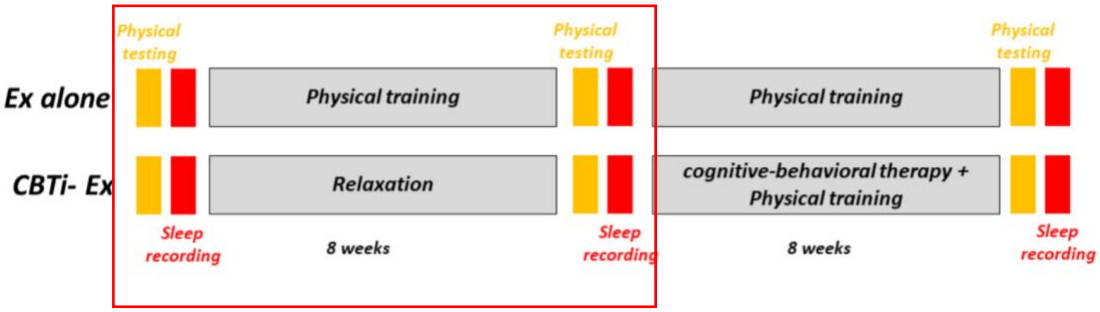

Figure 1. Study Design for APNex Pilot Trial, with a red box to represent the section of the larger study that this thesis focused on

5.2 Subjects

5.2.1 Recruitment and Screening

The study sample comprised 16 participants with COMISA who completed the first phase of the intervention study. Recruitment was through poster advertisements in the Concordia PERFORM email server and newspaper advertisements. Interested potential participants underwent three levels of screening to determine eligibility; phone screening, a diagnostic interview, and polysomnography recording. Interested participants were first screened over the phone to assess general eligibility. If included, they took a semi-structured diagnostic interview (SCID) to determine insomnia disorder diagnosis and any other potential physical or mental disorders. After the SCID, participants underwent a night of polysomnography recording (PSG) to determine the presence of OSA and rule out other sleep disorders. If the participant was eligible, the PSG night also served as an acclimation night, to get the participant comfortable with sleeping

in the lab environment and to reduce the "first night effect"[127] before their first pre-intervention EEG measurement night.

5.2.2 Inclusion Criteria

Included participants were required to have a diagnosis of insomnia disorder, defined as having trouble falling asleep (taking at least 30 minutes to fall asleep), problems maintaining sleep (waking up three or more times per night or waking up for over 30 minutes in the night), and/or difficulty staying asleep (waking up thirty minutes or more before their desired wake time), at least three times per week for at least three months, as defined by the ICSD-3. Participants also were required to have a diagnosis of OSA from a clinician, confirmed by the PSG night with an AHI between 5 and 30 per hour. For ethical reasons, participants must have had the opportunity to try CPAP before enrolling in this study. Use of a CPAP machine was not mandatory in this study, as not all participants choose to use one. Participants who decided to use the CPAP machine for the duration of the study must have been using the CPAP for over three months prior to the start of the study, or they were put on a waitlist until the three months have passed. This was intended to account for the acclimation period to the machine.

5.2.3 Exclusion Criteria

Participants were excluded from the study if they had any other sleep disorder, such as: narcolepsy, restless leg syndrome, or REM sleep behaviour disorder, or any chronic medical condition which would affect their ability to participate in exercise training. Medical conditions which excluded potential participants included: stroke, heart problems (myocardial infarct, heart failure, heart surgery, pacemaker, etc.), diabetes, cancer treatment in the last 2 years, schizophrenia

or bipolar disorder, epilepsy, neurological disease (e.g., multiple sclerosis, Parkinson's disease, dementia), major surgery in the last 3 months, alcohol or drug abuse, being pregnant or breastfeeding, and any contraindication for exercise based on the Physical Activity Readiness Questionnaire (PAR-Q) and medical clearance form. Individuals taking hypnotic medications were advised to stop use for at least two weeks before baseline assessments and commit to not use medication throughout the duration of the study and post-treatment assessments. Lastly, individuals reporting participating in over 150 minutes per week of moderate-to-vigorous physical activity were excluded, with the aim being to include those who would benefit most from an exercise program.

5.3 Interventions

5.3.1 Exercise-training Condition

Participants who were randomly assigned to the exercise-training condition participated in 60-minute sessions of structured moderate intensity aerobic exercise training combined with individualized resistance training, three times per week. The aerobic training consisted of 5 minutes warm up, followed by 40 minutes of aerobic exercise (walking, cycling, running... etc) performed at the heart rate (HR) associated with the ventilatory threshold (determined from the prior cardiorespiratory fitness test), and finally 5 minutes of cool down. Resistance training consisted of one set of 12-15 repetitions for 6-8 different exercises. Of the three weekly training sessions, one was administered at the PERFORM Centre at Concordia University under the direct supervision of a trained exercise physiologist. The other two weekly sessions were unsupervised, taking place at the participant's home or community. Participants logged these workouts and were called weekly for follow up and to ensure adherence to the program.

5.3.2 Relaxation Condition

Relaxation training involved self-guided sessions of digital audio recordings at least three times per week. There were four relaxation audio recordings consisting of: information on stress and relaxation, diaphragmatic breathing exercises, progressive muscle relaxation, and guided imagery. Relaxation therapy is associated with improvement in insomnia treatment with a small-to-moderate effect size[67]. However, we expected to see no effect of relaxation therapy on cardiopulmonary fitness.

5.4 Assessments

5.4.1 Questionnaires

On sleep assessment nights upon arrival, participants filled out the Insomnia Severity Index (ISI). ISI scores were analyzed as a primary objective of the study. The ISI is a validated and widely used self-report questionnaire, containing 7 items scored from 0 to 4 to examine the severity and impact of insomnia[128]. Items are added for a total score. A total score from: 0-7 indicates an absence of insomnia, 8-14 indicates sub-threshold insomnia, 15-21 indicates moderate insomnia, and 22-28 indicates severe insomnia[129].

5.4.2 Sleep Assessments

A total of three overnight sleep assessments took place. First, as previously mentioned, a PSG night was planned to determine eligibility for the study and to act as an adaptation night. Once the participant had been accepted for the for the study, they came back to the PERFORM Centre Sleep

Laboratory for a baseline experimental PSG1 night. Finally, after the 8-week intervention, the participant returned to the sleep laboratory for an PSG2 night.

Screening PSG Night

The first PSG night included measurements of thoracic and abdominal respiration (with belts), nasal-oral thermocouple airflow, a snore sensor and transcutaneous finger pulse oximetry to screen for OSA. It included leg EMG electrodes to screen for restless leg syndrome, as an exclusion criterion. The PSG setup also included 12 scalp electrodes (Fpz (ground), F3, Fz, F4, C3, Cz, C4, Pz (reference), O1, O2, M1, and M2), with EOG, EMG, and ECG. Set up followed the 10-20 montage setting as recommended by the AASM. All recordings were sampled at 512 Hz using SOMNOscreen plus (Somnomedics, Germany). If participants had been using the CPAP machine for at least 3 months, they were allowed to use it for the in-laboratory PSG night, and the CPAP was plugged into the SOMNO box allowing for PSG recording of the CPAP airflow.

PSG Night 1 and 2

Both EEG measurement nights had a similar setup to the screening PSG night, but with slight changes. The EEG setup included measurements of thoracic and abdominal respiration (with belts), nasal-oral thermocouple airflow, a snore sensor and transcutaneous finger pulse oximetry to screen for OSA, and 14 scalp electrodes (Fpz (ground), F3, Fz, F4, C3, Cz, C4, Pz (reference), P3, P4, O1, O2, M1, and M2), with EOG, EMG, and ECG. No leg EMG was used for the EEG nights. EEG, EOG, and EMG data was used for scoring sleep stages and periods of wake, to determine sleep efficiency and supplemental objective sleep data.

Sleep Scoring

Sleep stages and arousals were scored offline according to AASM guidelines with re-reference electrodes on the mastoids[12]. Each night of sleep data underwent scoring by two independent researchers to confirm that scoring met the set guidelines. Sleep efficiency (total sleep time/ time in bed) was extracted and used as the objective sleep variable for the primary objective of this thesis. Additionally, descriptive statistics on: SOL, WASO, SFI, TST, and arousals per hour were extracted.

5.4.3 Body Mass Index (BMI)

Height and Weight were taken before every sleep measurement night by a certified nurse, and BMI was calculated from this information accordingly.

5.4.4 Cardiorespiratory Fitness

Cardiorespiratory fitness was measured at baseline and after the 8-week intervention by a symptom-limited cardiopulmonary exercise test on a cycle ergometer (Corvial, Lode, Groningen, The Netherlands). Pre-intervention, the exercise test was used to rule out any major cardiopulmonary comorbidities that would interfere with exercise participation (exclusion criterion). Cardiorespiratory fitness data pre- and post- intervention was used to assess changes in cardiorespiratory fitness with the interventions. The exercise tests followed the Jones protocol[130] and were administered by trained personnel in the Cardiopulmonary Suite at the PERFORM Centre. Measurements included resting, exercising, and recovering hemodynamic response (heart rate via electrocardiography and blood pressure via automated BP monitoring), gas exchange and ventilatory response (oxygen consumption, carbon dioxide excretion, minute ventilation), oxygen

saturation via pulse oximetry, inspiratory capacity, and ratings of perceived exertion and dyspnea (Borg scale). Data was collected using a cardiorespiratory diagnostic system (Medgraphics CardiO2 Metabolic Cart, MCG Diagnostics, Saint Paul, MN, USA). Exercise capacity was defined as the maximal workload (in Watts) achieved and maintained for at least 30 seconds. Peak oxygen consumption was averaged from the last 30 seconds of the testing phase. The workload, oxygen consumption, and heart rate at which the ventilatory threshold occurred were identified using the V-slope approach[131]. For this thesis, focus was on measurements of peak oxygen consumption (VO_2 peak), VO_2 at the ventilatory threshold, and heart rate (HR) at 50% isotime.

Exercise Test Interpretations

ISO time

Due to varying test durations within and between participants, and the need to compare the same absolute time points within participants, isotime (ISO) was used. ISO can be defined as the longest duration for which data are available across all exercise tests completed by a given participant. In this study, with two time points (pre-treatment and post-treatment), ISO corresponded to the shortest test duration of the two achieved by a single participant. We used ISO to then segment the duration of the shorter test in 25% increments, to compare to increments of the same length of time in the longer test, allowing us to compare data at the same time point within the same participant pre to post. For example, if participant A completed an exercise test in 5 minutes pre-treatment and 8 minutes post-treatment, ISO was 5 minutes. Therefore, 50% of ISO within this same participant would be at 2.5 minutes for both tests taken. For this thesis, heart rate at the 50% ISO was used as a variable corresponding to cardiorespiratory fitness level.

VO_2 Peak and Heart Rate

VO_2 peak (in ml/kg/min and in L/min) and heart rate (in bpm) obtained during the exercise test were averaged over 30 seconds at the following time points: rest, warmup, 25% ISO time, 50% ISO time, 75% ISO time, and peak ISO time. VO_2 peak as a percent of normal predicted value was also obtained.

VO_2 at VT

Ventilatory threshold was determined manually by two certified kinesiologists using the V-slope approach. The VO_2 achieved at that threshold (VO_2 at VT) was recorded and used as a measure of cardiorespiratory fitness.

5.5 Data Analysis and Statistics

5.5.1 Statistics

Statistical analyses were performed using IBM SPSS Statistics software (version 26, New York, United States). Level of significance was set at $P < 0.05$.

5.5.2 Participant Demographics

Participant demographics were examined using descriptive statistics of mean, median, minimum and maximum values, and standard deviations. Due to the small sample, visual inspection was used to determine normality of the data.

VO_2 peak values, extracted from baseline exercise tests, were compared to normal age-predictive values, to better understand the exercise capacity of our sample in relation to a healthy population and to previous reports of individuals with OSA alone. Linear regression equations were used to determine the age predicted VO_2 (ml/min) for healthy sedentary individuals. The linear regression equation for males is; Weight x [50.75 - 0.372 x (Age)], based on healthy males

from 18 to 72 years of age not including the veteran population[132]. The linear regression equation for the females is; (Weight + 43) x [22.78 - 0.17(Age)], based on individuals over 35 years old, with a lack of symptomatic coronary artery disease and BMI of 27.4 ± 5.7[133].

5.5.3 Objective 1

To assess the primary objective of the study, two-way repeated measures ANOVAs, with time (baseline vs. post-8 weeks) as the within-group factor and condition (exercise vs. relaxation) as the between-group factor, were conducted to examine the impact of treatment program on ISI score and on sleep efficiency. Time, condition, and time by condition interactions were examined using Greenhouse-Geisser conservative degrees of freedom. Due to the fact that no previous study has examined the effects of an exercise intervention on insomnia severity in a COMISA population, Cohen's d effect sizes were calculated for each group.

5.5.4 Objective 2

To assess the secondary objective of the study, a repeated measures ANOVA with time (baseline vs. post-8 weeks) as a within-subject factor and condition (exercise vs. relaxation) as a between-subject factor was used. Additionally, the interaction between time and condition was examined for the outcome variables of peak oxygen consumption (VO_2 peak)(ml/kg/min)(L/min), heart rate (HR) at 50% ISO time (bpm), and VO_2 at the ventilatory threshold (VT)(ml/kg/min)(L/min). Tests of simple main effects were used to specify main and interaction effects.

5.5.5 Objective 3

To determine whether a change in cardiorespiratory fitness was associated with changes in subjective measures of insomnia, a Spearman's bivariate correlation between change in

cardiorespiratory fitness (represented by VO_2 max, HR at 50% ISO, and VO_2 at VT) and change in ISI scores was conducted for n=8 participants in the exercise group.

5.5.6 Supplemental Analyses

Supplemental ANOVAs with time (baseline vs. post-8 weeks) as a within-subject factor and condition (exercise vs. relaxation) as a between-subject factor, were conducted to determine time, condition, and time by condition interactions for the following objective measures of sleep: SOL, WASO, SFI, TST, and arousals (per hour).

To further examine subjective measurements of sleep, Spearman's Rho correlations were conducted on baseline values of PSQI, ESS, and ISI scores. Additionally, repeated measures ANOVAs with time (baseline vs. post-8 weeks) as a within-subject factor and condition (exercise vs. relaxation) as a between-subject factor, were used to examine any time, condition, and time by condition effects on PSQI and ESS scores.

6. Results

6.1 Population Characteristics

The consort flow diagram is presented in Figure 2. Of the 21 eligible participants, 16 were randomized, and 15 completed the post-treatment assessments. One individual did not complete the post 8-week ISI questionnaire. For medical reasons, one participant completed their post 8-week CPET on a treadmill, rather than the cycle ergometer, rendering workload useless.

Of the participants in the exercise group, the mean total number of exercises completed was 24 (SD = 6.6, range = 13-35) out of a possible maximum of 24 (three exercise sessions per week for eight weeks). Of the participants in the relaxation group, the mean total number of

relaxation sessions completed was 41 out of 24 (SD =31, range =14-97), as some individuals chose to do more than the recommendation of three sessions per week. Five completed all relaxation sessions. Adherence data was missing for one participant.

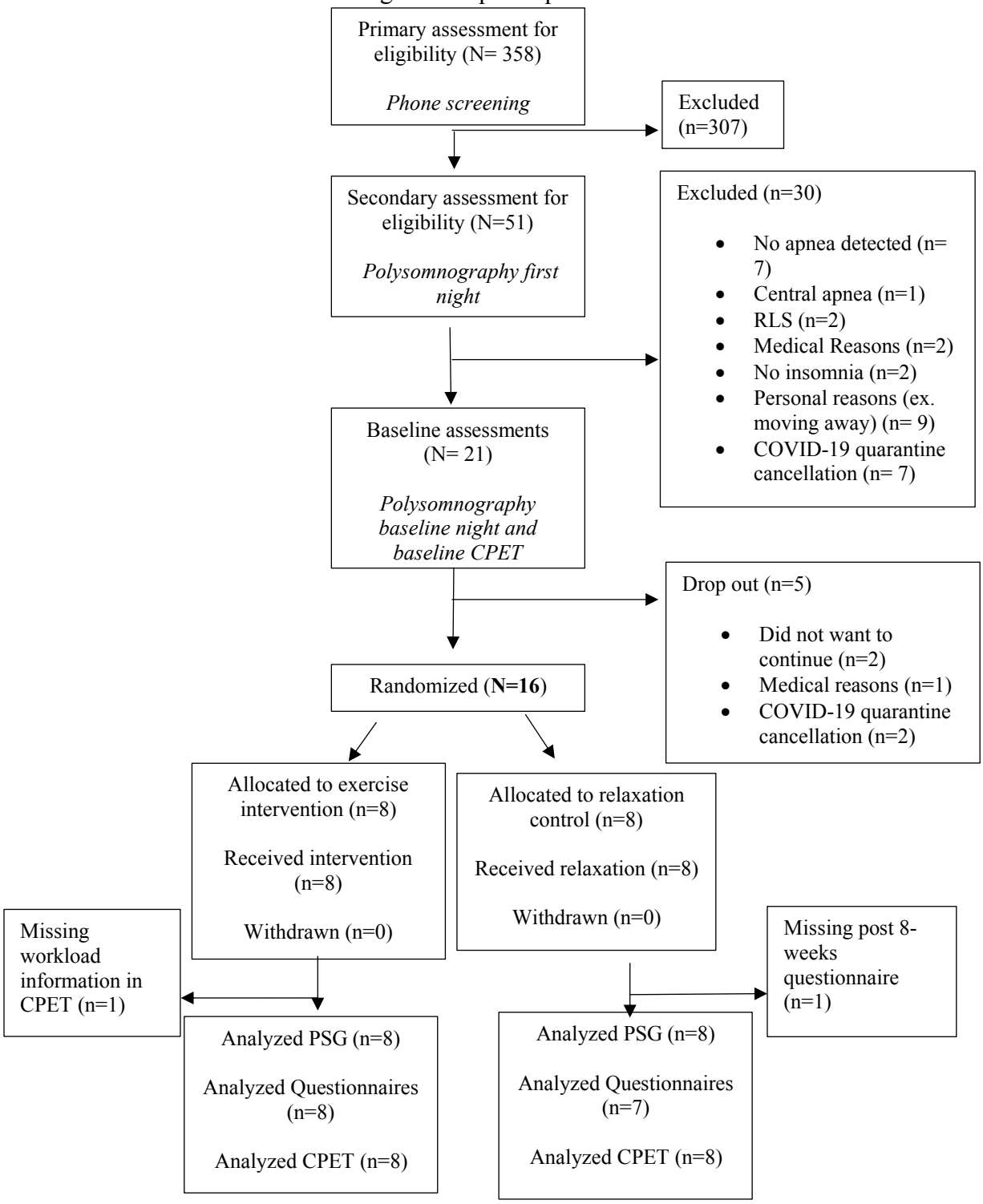

Figure 2: Participant Flow Chart

6.2 Participant Demographics

Participant demographics, baseline measures of cardiorespiratory fitness, and group differences can be found in Tables 2 and 3. Sixteen participants were randomized (10 females (F), 6 males (M)), ranging in age from 29-70 years, with the mean being 54.9 ± 13.4 years of age. About 11 (69%) participants used CPAP throughout the study. Eight participants were randomized to the exercise group (5F, 3M), and eight to the relaxation group (5F, 3M). The mean baseline VO_2 peak as a percent of normal predicted value was 87% ± 16.6, with seven participants failing to reach 85% of the age-predicted maximal value (See Figure 3).

Independent samples t-tests showed no significant differences between groups at baseline for the following baseline measurements: age, BMI, ISI, SE, HR_{rest}, HR at 50% ISO, VO_2 at VT, VO_2 peak, SOL, WASO, TST, SFI, and for the number of arousals per hour.

Variable	Range (min-max)	Mean	Median	SD	Group difference
Age	29-70	54.9	58	13.4	0.068
Sex	10F; 6M	n/a	n/a	n/a	n/a
CPAP Use (percent of users)	69%	n/a	n/a	n/a	n/a
Baseline BMI	17.9-54.2	31.7	28.8	8.86	0.105
Post- 8 weeks BMI	17.4-55.1	31.2	29.7	8.90	0.137

Table 2: Demographics for all participants (N=16), with group differences reported as p values calculated using independent samples t-tests

Variable	Range (min-max)	Normal? (Y/N)	Mean	Median	SD	Group Difference
Baseline Resting HR	60-108	N	75.00	74.25	11.46	0.354
Post- 8 weeks Resting HR	47.28-104.71	Y	72.26	70.21	12.34	0.114
Baseline HR at 50% ISO	79.83-136	Y	104.37	104.25	14.25	0.592
Post-8 weeks HR at 50% ISO	78.25-141.55	Y	102.58	103.78	17.18	0.257
Baseline VO2 Max (L/min)	0.92-4.18	N	1.87	1.70	0.88	0.147
Post- 8 weeks VO2 Max (L/min)	0.96-3.79	Y	1.95	1.87	0.80	0.558
Baseline VO2 Max (ml/kg/min)	13.23-43.21	N	20.53	19.19	7.95	0.879
Post- 8 weeks VO2 Max (ml/kg/min)	14.34-40.49	Y	22.20	20.84	7.20	0.266
Baseline VO2 at VT (mL/kg/min)	7-21	Y	12.38	11.55	3.62	0.665
Post- 8 weeks VO2 at VT (mL/kg/min)	8.8-19.64	Y	13.11	13.2	3.22	0.511
Baseline Workload Max	80.00-367.33	Y	153.80	146.71	76.21	0.114
Post- 8 weeks Workload Max	64.13-332.13	Y	159.21	128.07	79.34	0.160
Baseline VO_2 peak (% of normal predicted value)	58.2-126.8	Y	86.9	84.6	16.6	0.445
Post- 8 weeks VO_2 peak (% of normal predicted value)	61.9-136.4	Y	92.2	84.5	21.5	0.013*

Table 3: Exercise variables for all participants (N=16), with group differences reported as p-values calculated using independent samples t-tests

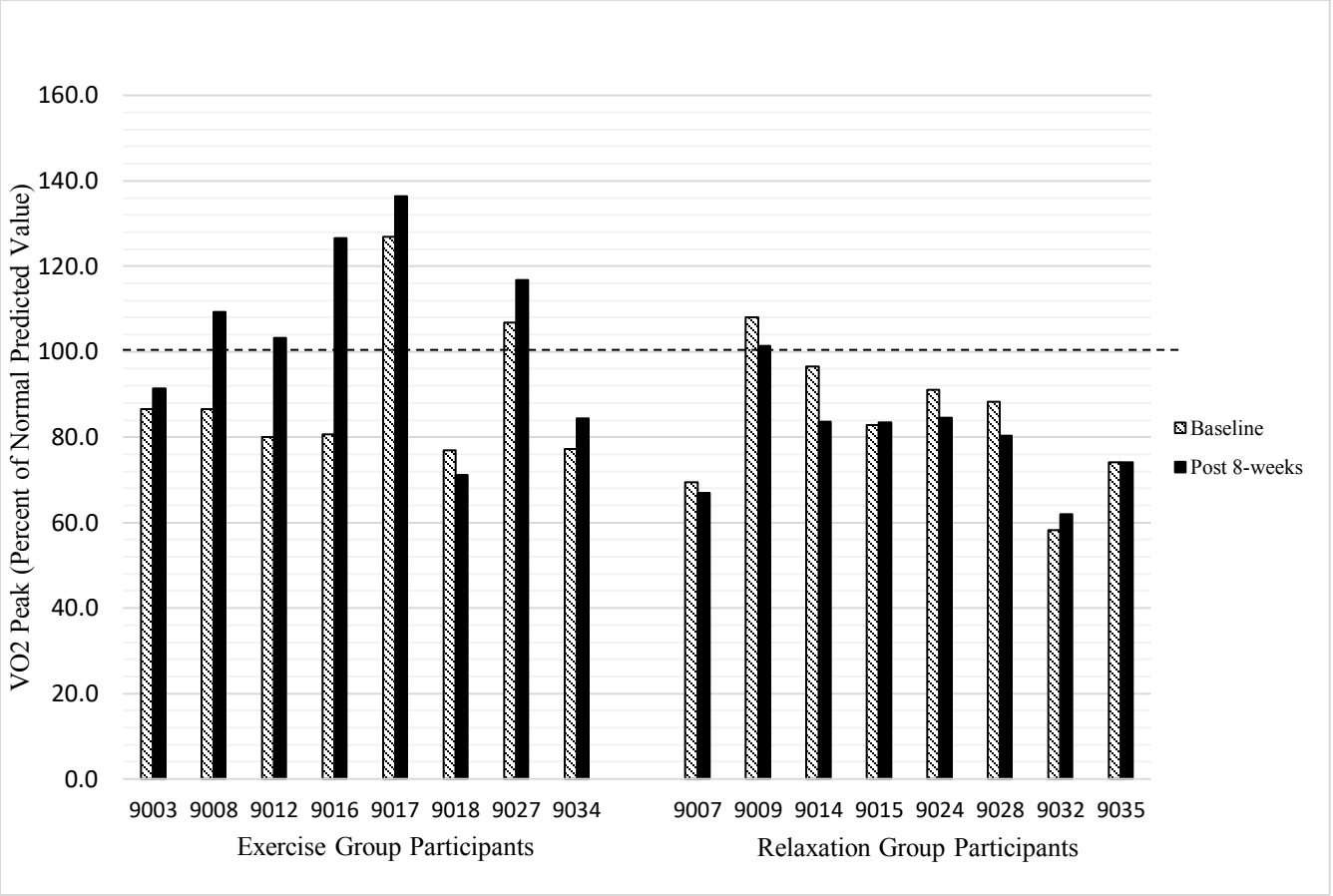

Figure 3: Baseline and post 8-weeks VO2 peak as a percent of the normal predicted value for exercise and relaxation groups

6.3 Objective 1

6.3.1 Insomnia Severity Index

The ANOVA yielded a significant effect of time on ISI score ($F(1,14)= 12.315$; $p= 0.003$). There was no significant effect of condition ($F(1,14)= 0.084$; $p= 0.776$) or time by condition interaction ($F(1,14)= 2.195$; $p=0.161$) (See Table 4). The effect size of both treatment conditions on ISI was large, with exercise showing a larger effect (Cohen's $d= 3.88$) than relaxation (Cohen's $d= 0.184$). The mean reduction in ISI score for the exercise group was 4.00 points, and the mean reduction for the relaxation group was 1.88 points. All eight participants in the exercise group and 5 out of 7 participants in the relaxation group showed improved their ISI (i.e. lower scores) post 8-weeks (See Figure 4a and 4b).

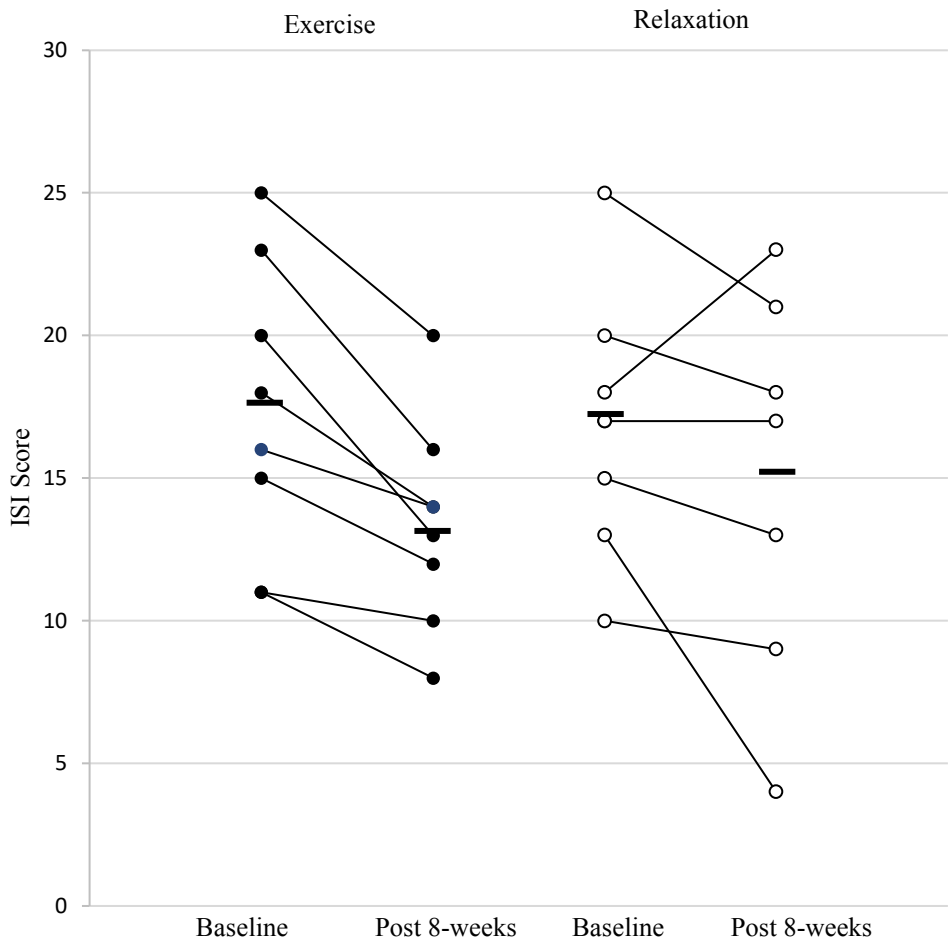

Figure 4a: Baseline and post 8-weeks ISI scores for exercise and relaxation groups

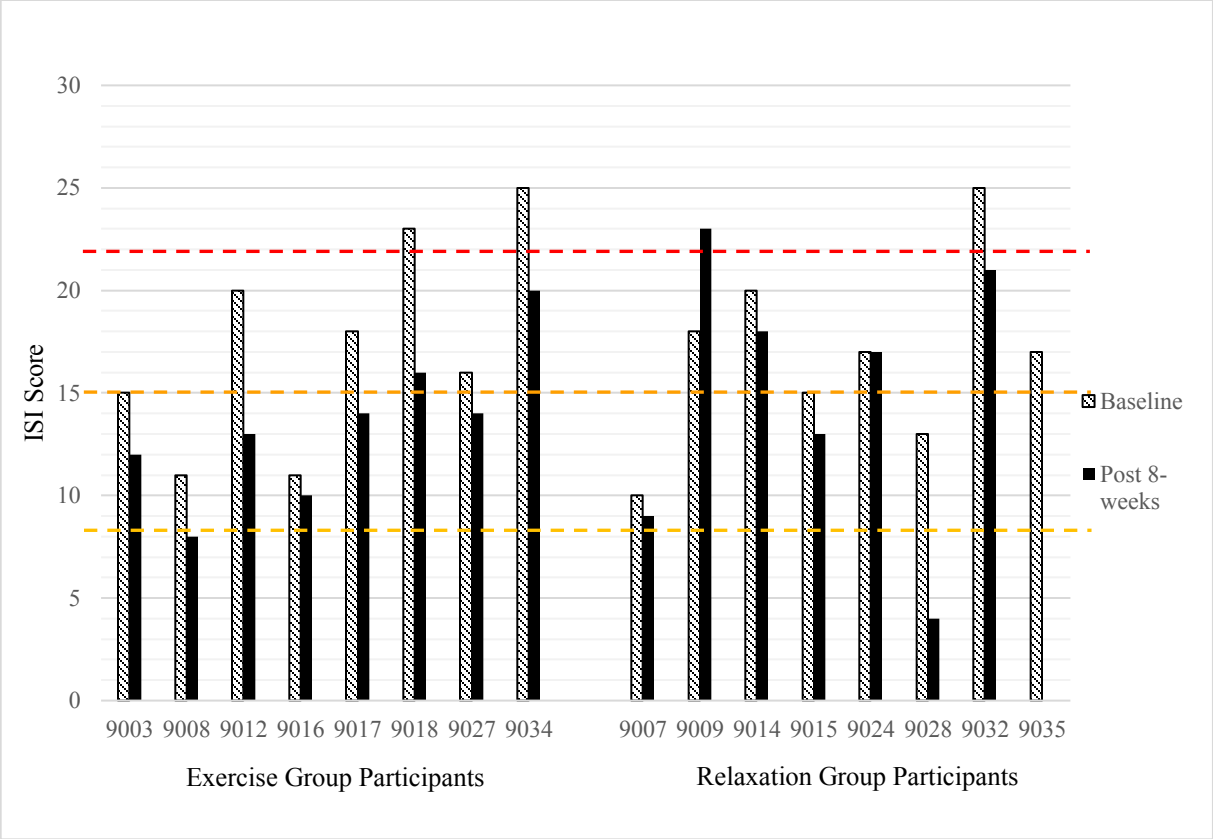

Figure 4b: Baseline and post 8-weeks ISI scores for individual participants in exercise and relaxation groups, with insomnia severity category indicated by yellow (sub-threshold (8-14)), orange (moderate (15-21)), and red (severe (22-28)) dotted lines

6.3.2 Sleep Efficiency

The repeated-measures ANOVA yielded no effect of time ($F(1,15)=0.601$; $p=0.451$) or condition ($F(1,15)=1.322$; $p=0.269$) on SE. Time by condition interaction also had no significant effects ($F(1,15)=0.898$, $p=0.359$) (See Table 4). There was no effect of the exercise intervention (Cohen's $d= 0.13$), and a medium effect of the relaxation intervention (Cohen's $d= -0.79$) on SE.

6.4 Objective 2

6.4.1 VO_2 Peak

The ANOVA yielded no significant main results for time on VO_2 peak (L/min) ($F(1,15)=1.456$; $p=0.248$) or VO_2 peak (mL/kg/min) ($F(1,15)=2.431$; $p=0.141$). There were no significant effects of condition on VO_2 peak (L/min) ($F(1,15)=1.973$; $p=0.182$) or VO_2 peak (mL/kg/min) ($F(1,15)=0.063$; $p=0.805$). There was a significant time by condition interaction for VO_2 peak (L/min) ($F(1,15)=7.604$; $p=0.015$) and VO_2 peak (ml/kg/min) ($F(1,15)= 10.724$; $p= 0.006$) (See Table 4). A large effect of the exercise intervention was found for VO_2 peak (mL/kg/min) (Cohen's $d=1.75$) and VO_2 peak (L/min) (Cohen's $d=1.47$). Post-hoc simple main effects paired t-tests for the exercise group showed a significant change in VO_2 peak (L/min) ($p= 0.059$), and VO_2 peak (ml/kg/min) ($p= 0.034$) over time. For the relaxation group, simple main effects tests showed no significant changes over time for VO_2 peak (L/min) ($p= 0.144$), or VO_2 peak (ml/kg/min) ($p=0.062$). See Figure 5 for VO_2 peak values at baseline and post-intervention for both groups.

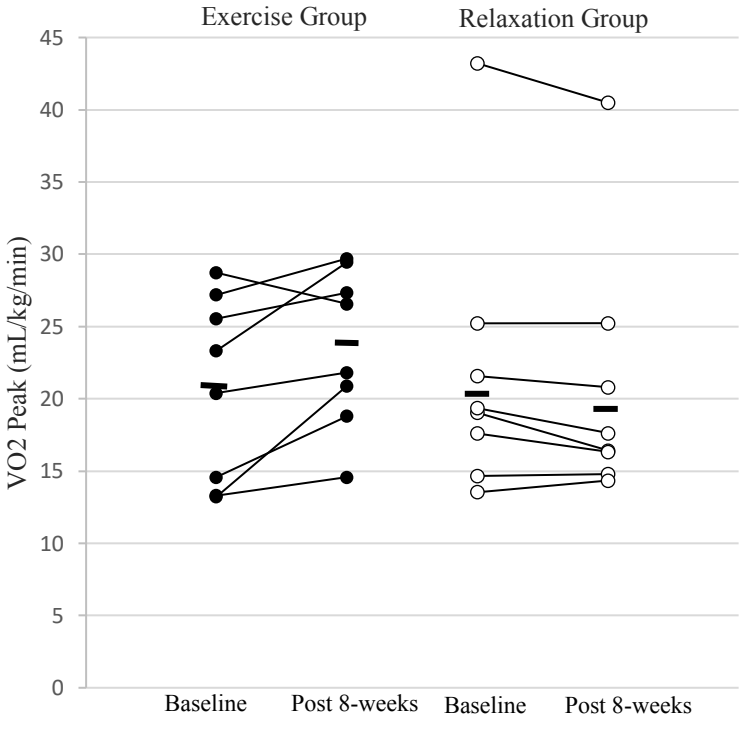

Figure 5: Baseline and post 8-weeks VO_2 peak for exercise and relaxation groups

6.4.2 HR at 50% ISO

The ANOVA yielded no significant main results for time ($F(1,15)=2.553$; $p=132$) or condition ($F(1,15)=0.780$; $p=0.392$). There was a significant time by condition interaction ($F(1,15)=7.667$; $p= 0.015$) (See Table 4). A large effect of the exercise intervention was found (Cohen's $d=1.48$). Post-hoc simple main effects paired t-tests for the exercise group showed a significant change over time ($p= 0.002$). For the relaxation group, simple main effects tests showed no significant changes over time ($p= 0.535$).

6.4.3 VO_2 at VT

The ANOVA yielded no significant main results for time on VT (L/min) ($F(1,15)=0.591$; $p=0.455$) or VO_2 at VT (mL/kg/min)($F(1,15)=1.966$; $p=0.183$). There were no significant effects of condition on VO_2 at VT (L/min) ($F(1,15)=1.844$; $p=0.196$) or VO_2 at VT (mL/kg/min)($F(1,15)=0.006$; $p=0.940$). No significance in time by group interaction was found for VO_2 at VT (L/min) ($F(1,15)=0.005$; $p=0.947$) and VO_2 at VT (ml/kg/min) ($F(1,15)=2.634$; $p=0.127$) (See Table 4). A large effect size of the exercise intervention (Cohen's $d= 0.87$) was found for VO_2 at VT (ml/kg/min) with no effect found for VO_2 at VT (L/min).

6.5 Objective 3

Spearman's Rho bivariate correlations between change in ISI ($ISI_{post\text{-}8\ weeks} - ISI_{baseline}$) and change in HR at 50% ISO ($HR_{post\text{-}8\ weeks} - HR_{baseline}$), VO_2 at VT (L/min) (VO_2 at $VT_{post\text{-}8\ weeks} - VO_2$ at $VT_{baseline}$), and VO_2 at VT (mL/kg/min) (VO_2 at $VT_{post\text{-}8\ weeks} - VO_2$ at $VT_{baseline}$) among the exercise group ($n=8$) showed non-significant associations (respectively, $r=-0.19$; $r=0.048$; $r=0.024$; $p>0.05$). Spearman's bivariate correlations between change in ISI and change in VO_2 peak (L/min) (VO_2 $peak_{post\text{-}8\ weeks} - VO_2$ $peak_{baseline}$) and VO_2 peak (mL/kg/min) (VO_2 $peak_{post\text{-}8\ weeks} - VO_2$ $peak_{baseline}$) among the exercise group showed weak correlations and no significance (respectively,

r=0.5; r=0.59; p>0.05). We also ran correlations for all participants as a whole group (N=16) and saw no significant correlations.

6.6 Supplemental Data

The ANOVA yielded no significant main results for time on: SOL (F(1,15)= 3.927; p=0.068), WASO (F(1,15)=0.003; p=0.955), SFI (F(1,15)=1.575; p=0.955), TST (F(1,15)= 0.421; p=0.527). There was; however, a significant main effect of time on Arousal (F(1,15)= 6.114; p=0.027). The ANOVA yielded no significant main results for condition on: SOL (F(1,15)= 0.029; p= 0.867), WASO (F(1,15)= 2.657; p=0.125), SFI (F(1,15)= 1.187; p= 0.294), TST (F(1,15)= 0.145; p= 0.710), or Arousal (F(1,15)= 1.703; p=0.213). The ANOVA yielded no significant interaction results for: SOL (F(1,15)= 0.274; p=0.609), WASO (F(1,15)= 0.038; p= 0.848), SFI (F(1,15)= 0.164; p= 0.691), TST (F(1,15)= 0.005; p= 0.945), or Arousal (F(1,15)= 0.358; p= 0.559). See Table 4 for all supplemental data results.

7. Discussion

To examine the effects of exercise training in comparison to a relaxation treatment on insomnia symptoms in individuals with COMISA, we randomized 16 individuals into two groups; one receiving exercise treatment (n=8) consisting of 3x60-minute sessions of moderate intensity aerobic and resistance training per week and the other receiving relaxation therapy (n=8) consisting of self-guided relaxation 3 times per week for 8 weeks. We collected data from PSG (SE), questionnaires (ISI) and CPET (VO_2 peak, VO_2 at VT, and HR at 50% ISO) at baseline and after 8 weeks of treatment. As a primary objective, we aimed to examine whether insomnia severity, represented by ISI results, or PSG-measured sleep efficiency, improved within and between groups. Primary objective results revealed a significant effect of time (pre,

post 8-weeks) on ISI score, but no significant effect of condition (exercise, relaxation) or time*condition interaction. Both exercise and relaxation showed large effect sizes for the reduction in ISI scores from pre- to post-treatment. Although the exercise intervention led to a larger effect size than the relaxation condition, the time*condition interaction was not statistically significant. No significant effects were found for SE. Our secondary objective involved examining whether exercise treatment had an effect on cardiorespiratory fitness, measured by VO_2 peak mainly, and also HR at 50%ISO and VO_2 at the VT. Results indicated a significant time*condition interaction for VO2 peak (ml/kg/min) and HR at 50% ISO (bpm), but not for VO_2 at VT, indicating that significant changes in cardiorespiratory fitness occurred in the exercise group but not the relaxation group. Our final aim was to examine whether any changes in insomnia severity correlated with changes in fitness. For this, Spearman correlations indicated no significant correlation between change in ISI and change in VO2 peak (ml/kg/min).

7.1 Primary Objective: ISI and SE

The results on self-reported insomnia severity were in-line with the primary hypothesis, that both groups would experience a reduction in insomnia symptomology, represented by reduced ISI, with a greater change in the exercise group than the relaxation group. Although the time by group interaction was not significant, the effect sizes of exercise on ISI was larger than that of relaxation. While ISI scores showed trends in line with the hypothesis, sleep efficiency, determined by PSG recordings, did not show similar findings. Indeed, there was no change in objective sleep efficiency after both interventions.

While this study is the first to examine exercise training as an intervention for the COMISA population, these results support previous literature examining exercise as an intervention to improve insomnia severity in individuals with chronic insomnia. Literature

examining individuals with insomnia alone, have found changes in subjective insomnia symptomology, with mixed results on objective sleep changes. An RCT on inactive adults (40 years and older) with chronic insomnia by Hartescu et al.[134], administered an exercise intervention involving 5 x 30-minute brisk walking sessions (at least 150 minutes of moderate to vigorous physical activity) per week for 6 months, in comparison to a control condition of usual activity level, and found a similar decrease in insomnia severity. An average 4-point reduction in ISI in the exercise group was found compared to an average reduction of 1.4 points in the control group ($p=0.03$). Similarly, our ISI results are in-line with those found in an RCT by D'Aurea et al. examining 4 months, 3 times per week, of 1-hour resistance exercise sessions, stretching sessions, or control (no treatment) on 28 individuals with chronic insomnia[124]. Resistance and stretching conditions improved insomnia symptomatology significantly compared to a control group. Similar to our study, no significant changes in PSG data were found[124]. While existing literature has examined insomnia populations (not COMISA), and contain several varying modalities of exercise, patterns of ISI improving with exercise along with non-significant changes in PSG variables are emerging and are consistent with the findings of this thesis.

In individuals with OSA alone, exercise-intervention RCTs have examined subjective quality of sleep and daytime fatigue using the PSQI[93,99] and ESS[93,100,118], but not the ISI. Of these studies, only one found a significant improvement in subjective daytime sleepiness (ESS)[135], and of the two studies examining PSQI, both found significant decreases in the global PSQI score post-trial[93,99]. Research examining objective sleep data exercise intervention RCTs on OSA, have reported improvement in SWS[101], number of arousals[93,101], SE[114], and TST[117] (measured by PSG) after an exercise intervention, but these findings are inconsistent across the literature. An emerging pattern in previous studies on individuals with each disorder alone, which involves more consistent

changes in subjective sleep than objective PSG data after an exercise intervention, is consistent with the findings of this thesis. This yields an important question regarding the mechanism of the effects of exercise treatment on subjective sleep.

7.1.1 Potential Mechanisms

The behavioural model of insomnia, originally proposed by Spielman et al.[136], states that insomnia occurs in response to predisposing, precipitating, and perpetuating factors. Predisposing or trait factors include biological factors such as hyperarousal, which would put an individual at a higher risk of experiencing insomnia symptoms. Precipitating factors are factors which trigger the onset of insomnia, such as life stress or sleep schedule changes. Perpetuating factors are psychological factors, such as worry or rumination, which would contribute to the persistence of insomnia[136,137]. Mechanisms by which exercise and relaxation may have had an effect on insomnia symptoms, include effects on trait factors, by influencing biological factors such as arousal, and effects on precipitating factors, such as life stress and mood. A key finding of this thesis was the greater effect size found for both exercise and relaxation on our subjective measure (ISI) but not on objective PSG data (SE).

The discrepancies between PSG data and subjective reports of sleep quality and quantity observed in this thesis, have been previously observed in individuals with insomnia alone. This paradox has been referred to as sleep-state misperception[138–140]. Mechanisms underlying sleep-state misperception may involve psychological, cognitive and physiological factors[141]. Based on the results of this study, we will be exploring mechanisms which have been previously associated with sleep misperception and which may be altered by both exercise and relaxation, but to a greater degree exercise. The trait factors of autonomic function and brain derived neurotrophic factor

(BDNF) and precipitating psychological factors such as mood will be further examined as potential mechanisms.

HPA Axis and cortisol

The mechanism by which we observed a change in subjective but not objective sleep with exercise, may be involving changes in the HPA axis activity. Both OSA and insomnia may be related to HPA axis dysregulation. One existing theory is that insomnia is partially caused by HPA hyperreactivity. Also, in OSA, HPA axis hyperreactivity has been observed and may be a consequence of the disorder[142]. Previous research suggests that activity of the HPA axis is associated with individuals' sleep perceptions, being associated with subjective measures of sleep quality but not objective [142–144].

The HPA axis releases the stress hormone cortisol, which displays a circadian rhythm increasing around waking and steadily decreasing throughout the day[145]. Cortisol shows a strong awakening response, with variability between sleep onset and awakening being associated with measures of subjective sleep but not objective.[146] Cortisol could be one mechanism by which our study revealed subjective effects of the exercise intervention, but not objective effects.

Evidence of serum cortisol levels changing with chronic exercise are mixed, with some studies finding significant decreases in cortisol following an exercise intervention[82,147–151], and others finding no significant changes in cortisol with exercise[152]. Of these studies, only one has examined changes in plasma cortisol with an exercise intervention in individuals with insomnia[82]. This study examined 21 sedentary participants (ages 44.7 ± 9 years) with chronic primary insomnia over 4 months of a moderate aerobic exercise training and found a significant decrease in cortisol post-intervention compared to baseline (P=0.02). More studies need to be conducted on the effects

of exercise on serum cortisol in individuals with insomnia and/or COMISA before conclusions can be made regarding changes in cortisol affecting the HPA axis and subjective sleep in our study.

Previous literature suggests that various forms of relaxation training, such as focused attention meditation[153], progressive muscle relaxation[154], integrative meditation[155], Buddhist meditation[156], and mindfulness interventions[157] also decrease basal cortisol levels, with a greater effect on more at-risk populations[145]. Cortisol may thus be one mechanism through which relaxation improves subjective insomnia severity. While it was outside the scope of this thesis, future studies within this lab could examine within-subject and between-group changes in cortisol and any potential associations with subjective ISI scores and objective EEG measures of SE.

BDNF

Another potential mediator of the effect of our exercise intervention on subjective but not objective measures of insomnia severity in comparison to relaxation, is brain-derived neurotrophic factor (BDNF). BDNF is a protein involved in the growth, differentiation, and maintenance of neurons. BDNF has a role in the regulation of synaptic plasticity, aiding in memory and learning. Studies have shown decreased levels of serum BDNF in individuals with insomnia[158–162], with a significant correlation between severity of symptoms and lower levels of serum BDNF[158,159,161,162]. Research suggests that, while serum BDNF correlates with subjective insomnia symptomology (ISI scores), it does not correlate with objective EEG measures of sleep continuity[158]. One hypothesis for the link between BDNF and chronic insomnia is called the "neurotrophin hypothesis of depression" which states that stress-related mood disorders result from decreased BDNF induced by deregulation of the HPA axis by chronic stress[161,162]. While chronic stress can decrease BDNF levels, some studies indicate that acute stress, such as a single night of sleep deprivation,

can increase BDNF[161,162]. Exercise is also an acute stressor and has shown to increase BDNF in animal and human studies. A recent meta-analytic review examined the effects of three categories of exercise on BDNF in humans: an acute single exercise session, a single exercise session in individuals undergoing regular exercise of 3-24 weeks, and resting BDNF in individuals undergoing regular exercise ranging from 3 weeks to 2 years[163]. They found a moderate effect of acute exercise on BDNF, with an intensified effect in the group undergoing regular exercise, and a small effect of regular exercise on resting BDNF[163]. While the sample size of studies used in this meta-analysis was too small to examine exercise modality on BDNF, it supports the hypothesis that exercise increases BDNF levels in healthy human subjects. Previous literature has shown significant increases in BDNF with meditation interventions[164–166]; however, no study has examined BDNF with the same guided relaxation prompts used in this study. While several studies have examined the effects of exercise and meditation interventions on BDNF, to our knowledge, no study has compared effect sizes between these interventions. Since serum BDNF is highly correlated with subjective but not objective insomnia symptomology, and may be increased with exercise and relaxation, it could have played a potential role as a mediator between exercise and ISI scores within this study. Further research is necessary.

Psychological Factors

This underestimation of sleep in sleep-state misperception has been shown to be related to anxious-ruminative traits[167], poor stress-coping resources[167], anxiety[168] and depression[168]. Physical activity and relaxation treatments have both been shown to improve mood; thereby potentially affecting sleep-state misperception through mood alterations. It is well documented that exercise interventions can improve symptoms of depression and anxiety[169] in otherwise-healthy

participants, and to improve feelings of self-efficacy and stress in healthy individuals[170]. Worry is a key perpetuating factor in individuals with insomnia, and has been shown to improve after an exercise intervention in an RCT including 6 weeks of resistance or aerobic training in comparison to a wait-list control group[171]. Relaxation therapies such as mindfulness- based interventions have also shown to alleviate symptoms of anxiety, depression, stress, quality of life, and psychological or emotional distress[172]. Diaphragmatic breathing has been shown to improve mood, depression, anxiety, and stress[173,174]. Since effect sizes of both exercise and relaxation interventions on ISI in our study were large, changes in individuals' perceptions of sleep may have been related to changes in mood.

7.2 Secondary Objective: Exercise training on Cardiorespiratory Fitness

While research shows a decreased exercise capacity in individuals with OSA alone[175–177], no research has been done on exercise capacity in individuals with COMISA. In this study, baseline measurements of VO_2 peak were compared to the normative values for healthy sedentary individuals of the same age and sex, and to the literature on exercise capacity in people with OSA. At baseline, our participants' average VO_2 peak was 21.3 ± 7.8 ml/kg/min, corresponding to 87% ± 16.6 of their normal predicted value. This VO_2 peak is comparable to the average VO_2 peak found in individuals with an AHI > 30 [175], whereas our participants had an AHI of 5-30. These findings at baseline suggest that individuals with mild-to-moderate COMISA exhibit reductions in cardiorespiratory fitness comparable to those seen in people with moderate-to-severe OSA of a similar age and BMI. Baseline exercise tests for this study suggest that individuals with COMISA show a greater reduction in exercise capacity compared to previous literature on individuals with OSA.

The chosen modality of our exercise intervention was expected to enable improvements in fitness, based on research involving healthy participants and people with OSA[99]. Previous research on individuals with OSA and insomnia have shown different responses to a single bout of exercise, in comparison to healthy individuals. In individuals with primary insomnia alone, subjective daytime impairments experienced by some is associated with exercise capacity[76]. Previous research shows a reduction in exercise capacity and exercise tolerance in individuals with OSA alone in comparison to healthy individuals. Decreased VO2 peak[178], exaggerated blood pressure[179–181], delayed heart rate recovery[176,180], and an impaired cerebrovascular response to hypercapnia[182] have been observed in individuals with OSA; however, from existing literature, it is unclear whether exercise training would reverse these impairments found at baseline.

To study the effects of this exercise intervention of 3x60 minute moderate intensity aerobic and resistance training sessions per week for 8 weeks on cardiorespiratory fitness, we examined VO2 peak, VO2 at VT, and HR at 50% ISO pre- and post- intervention within and between the intervention groups. Time*interaction effects for VO2 peak and HR at 50% ISO were significant; however, VO2 at VT did not show significant changes. Given that directly measured VO_2 peak during maximal or symptom-limited cardiopulmonary exercise testing is the "gold standard" measure of cardiorespiratory fitness[183], these results indicate an effect of the exercise intervention on cardiorespiratory fitness level. Reasons for the lack of significant time*condition interaction effects on VO_2 at VT may be due to human error in the manual interpretation of VT in comparison to the automated VO_2 peak. Significant changes in VO_2 peak are indicative of participants in the exercise group having the capacity to exercise for a longer period of time and at a higher workload. Indeed, 7 out of 8 participants in the exercise group increased the duration of their test pre-treatment to post- 8 weeks, compared to 2 of the 8 participants in the relaxation group. There were

no significant changes in BMI with the intervention; however, BMI does not account for weight distribution. To ensure that changes in adiposity did not account for these results, future studies should examine waist and neck circumference as well. Overall, objective two results indicated that our sample showed a reduced exercise capacity at baseline, comparable to individuals with more severe OSA alone, and that our exercise training intervention was effective at improving cardiorespiratory fitness, based on VO_2 peak and submaximal HR, in these individuals.

7.3 Tertiary Objective: Correlation between change in fitness and ISI

To obtain a clearer picture on mechanisms involved in improving ISI scores, the tertiary objective of this thesis examined the relationship between the change in ISI scores and changes in VO_2 peak and HR at 50% ISO. No significant correlations were found. There was a weak negative correlation between changes in ISI score and changes in VO_2 peak, indicating that those who improved VO_2 peak the most, improved ISI score the least. This contradicts our hypothesis that improvements in ISI score (indicated by larger decreases in ISI change (post 8-weeks minus baseline)) would be correlated with improvements in change in VO_2 peak (indicated by an increase in VO_2 peak post 8-weeks minus baseline). This suggests that improvement in cardiopulmonary capacity did not explain the improvement in subjective insomnia severity observed in the present study. While we did not find a significant correlation, it is important to note that 8/8 participants in the exercise group showed decreased ISI scores post intervention, and 7/8 showed improved VO_2 peak; in return, 5/7 in the relaxation group improved ISI and 2/8 improved VO_2 peak, indicating that results showed trends in line with our hypothesis. Given the homogeneity of the response, with ISI and fitness improving in all but one exercise participant, correlational tests would require a high dose-response relationship to prove statistically significant. We cannot infer from these results further, as there is a lack of power due to the

small sample (n=8); however, future studies including larger samples would be beneficial to investigate whether it is the change in fitness influencing ISI or another factor involved with the increase of physical activity.

7.4 Limitations

Some limitations within this study must be addressed. The principal limitation of this study is its small sample size (N=16). Recruitment of clinical populations for behavioural interventions lasting several months poses as a challenge, especially with individuals with COMISA, since COMISA is less present in the general population than either disorder alone. Participant recruitment and in-lab assessments were also put to a halt due to COVID-19 beginning in March 2020. As a result of the small sample size, we lacked the power to conduct a covariate analysis including age, sex, BMI, and CPAP use. However, no significant differences were found between groups at baseline for age, BMI, ISI, SE, HR at 50% ISO, VO_2 at VT, VO_2 peak, SOL, WASO, TST, SFI, and for the number of arousals per hour.

Another limitation is that the post 8-week exercise test for one participant was conducted on a treadmill for health reasons, whereas all other tests were conducted on a cycle ergometer. It is well documented that individuals report higher VO_2 peaks during treadmill testing in comparison to cycle ergometer testing[184]. Therefore, the increase seen post-intervention for this individual may have been due to exercise testing modality rather than the exercise intervention. However, upon further inspection, if we were to remove this participant, the mean VO_2 peak post 8-weeks for the exercise group would increase to 24.3 ± 5.5 (instead of 23.6 ± 5.5), indicating that the post 8-weeks increase in mean VO_2 peak for the group was not impacted in the expected direction by the protocol change.

While the primary objective of this thesis was to examine effects on insomnia severity, it would have been valuable to also examine any potential changes in apnea severity, indicated by AHI. To accurately examine effects on AHI would have required participants to sleep without a CPAP machine, as the AHI data from the CPAP machine was unavailable to us. For ethical reasons we could not ask participants using CPAP at baseline to cease its use for the purpose of the study. Out of 16 participants, only 5 did not use a CPAP; therefore, we were underpowered to analyze AHI. Additionally, we were underpowered to compare results for CPAP users vs. non-users or to use CPAP use as a covariate for this study.

As with several studies of sleep utilizing PSG data, a limitation of this study involved the fact that only 3 overnight assessments were conducted (the first night, baseline assessment, and post 8-weeks), of which only the baseline and post 8-weeks data were used for analysis. The first night of PSG was used for screening purposes, but also to acclimate the participant to the new environment to avoid any "first night effect" on the baseline night. Since this thesis was taken as a part of a larger study, it was not feasible to examine the effects of exercise compared to relaxation on sleep assessed over a longer period of time. Future research would benefit from studies examining effects after 8 weeks, with a greater number of objective PSG collection time points.

Regarding adherence, weekly exercise sessions were recorded by weekly phone calls and exercise logs, while relaxation sessions were monitored by weekly calls alone. Objective measures of adherence in addition to our weekly calls and logs could have improved the reporting quality of this study. Exercise sessions could be monitored with fitness-tracking watches, and relaxation sessions could have been conducted "in-person" via online sessions. This could have improved the internal validity of our results by ensuring adherence.

For ethical reasons, we did not include a group receiving no treatment. Individuals with COMISA experience worse symptoms than those with insomnia or OSA alone[42,43]. We asked participants to avoid beginning using CPAP or other treatments, like pharmacotherapy, during this study period. For ethical reasons, it would have been difficult to ask participants in a control condition to avoid seeking help for 16 weeks, as this was a part of a larger, longer study. Also, we would have had increased difficulty recruiting participants and difficulty with participant adherence with a control condition of no treatment or waitlist. For these reasons, we compared the exercise intervention to relaxation, expecting that both groups would improve ISI but with different effect sizes. It is important to note that we are unable to rule out the possibility that the changes in ISI were due to natural changes over time rather than the specific intervention administered.

7.5 Strengths

Some strengths of this study include its RCT design, gold-standard measurements for sleep and cardiorespiratory fitness, blinding protocol, equal number of participants per group, and number of unsupervised sessions. Our study followed a randomized controlled trial design, with participants randomly assigned to the exercise or control relaxation condition. Another strength includes the use of both objective sleep measures (PSG) and subjective measures of insomnia severity (questionnaires), and gold-standard measurements for sleep variables (PSG) and cardiorespiratory fitness (CPET with direct measurement of VO2 peak). While we were limited in the number of participants, due to the difficulty recruiting and COVID-19 restrictions, our randomization by block allowed for the same number of participants in each group with the same number of males and females. Outcomes accessors in this study were blinded from participants' randomization. EEG night examinations were conducted by volunteers from the

sleep lab at Concordia University and by sleep technicians who were blinded to the condition of the subject. Exercise tests were conducted by kinesiologists in the cardiopulmonary suite at the PERFORM Centre at Concordia University who were blinded as well. One final strength of this study involved the fact that two of the three exercise sessions for participants were unsupervised. This allowed participants to continue their exercises at home during the COVID-19 pandemic, and this increased the external validity of the study in comparison to only using supervised sessions.

8. Significance and Conclusion

COMISA is a particularly complex disorder, with a difficult diagnosis process, numerous negative side effects, and sparse research available regarding its treatment. Individuals with COMISA suffer from more severe sleep disturbances, worse daytime functioning, lower quality of life, and higher rates of cardiovascular disease and depression than those with insomnia or OSA alone. Individuals with COMISA have a greater difficulty complying to the CPAP treatment for OSA and cannot use pharmacotherapy for their insomnia over the long-term due to the risk of worsening their side effects. Additionally, CPAP treatment alone will improve AHI, but not insomnia symptoms. An effective treatment option for both AHI and insomnia severity is crucial.

Exercise training has shown promising effects on sleep in populations of good sleepers, individuals with insomnia, and individuals with OSA. While the exact effects of exercise on sleep are inconsistent, and methodologies differ, evidence points to an effect on subjective sleep and AHI. To our knowledge, no RCT has examined exercise as a treatment for insomnia in individuals with COMISA, and this would be the first RCT to do so.

While we were underpowered in this pilot study to determine group differences, our results showed large effects of exercise and relaxation on ISI, with a larger effect of exercise treatment, supporting the original hypothesis and supporting previous studies conducted on individuals with insomnia alone. Sleep efficiency results from PSG data were nonsignificant, along with other supplementary objective measures of sleep quality, indicating that objective sleep quality was unchanged by either intervention. At baseline participants presented with cardiorespiratory fitness levels comparable to individuals with severe OSA, and our intervention involving aerobic and resistance exercise three days per week for 8 weeks led to significant improvements in cardiorespiratory fitness in these individuals. No association between VO2 peak and ISI was found in the exercise group.

The results of this thesis as a part of a larger pilot study, indicate a large effect size of exercise training on subjective insomnia symptoms. The question remains, whether exercise combined with CBTi would improve insomnia symptoms further in this population. Additionally, studies of a larger COMISA sample examining effects of exercise on both ISI and AHI, or exercise to improve ISI combined with CPAP to improve AHI, would be beneficial.

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Reference	Study Population	Sample Size	Control Group	Other Aspects of Intervention (if applicable)	Type of Exercise	Intensity	Exercise Session Duration	Exercise Frequency (per week)	Intervention Length	Sleep Measurement(s)	Main Sleep Results for Exercise Group
Singh et al., 1997[73]	Elders with depression	N=32	Health education		Supervised high-intensity progressive resistance training of the large muscle groups	80% 1RM	1 hour + 5 min stretching	3	10 Weeks	PSQI, Likert Scale of Subjective Sleep Quality and Quantity	Exercise significantly improved all subjective sleep quality measures compared to the control group
King et al., 1997[105]	Older adults with sleep complaints	N=43	Wait-list		Low-impact aerobic training	60-75% HRR	30-40 minutes	4	16 Weeks	PSQI	Significant ↓PSQI (↑Sleep Quality, ↑TST, ↓SOL) in exercise group compared to control group
Singh et al., 2005[100]	Adults with major and minor depression	N=60	General practitioner care	Participants randomized to one of three groups: supervised high intensity progressive resistance training (PRT), low intensity PRT, or general practitioner care	Progressive resistance training	**High:** 80% 1RM; **Low:** 20% 1RM	60 minutes + 5 minutes stretching	3	8 Weeks	PSQI	All groups significantly showed: ↓PSQI (↑sleep related QOL, ↓SOL, ↑sleep duration, ↑SE, ↓sleep dysfunction) with a significant effect favoring High over Low and GP groups
King et al., 2008[102]	Older adults with minor to moderate sleep complaints	N= 66	Health education		Moderate-intensity endurance exercise	60%–85% of HR max	1 hour supervised or 30 minutes at home	5 Total: 2 supervised, 3 on own	12 Months	PSG, PSQI, sleep diary	Relative to controls, the exercise group showed significant changes in: **PSG:** ↓%N1, ↑%N2, ↓awakenings during first third of the night; **PSQI:** ↓sleep disturbances, ↓PSQI; **sleep diaries:** ↓SOL, ↑feeling rested in the morning
Irwin et al., 2008[106]	Older adults with moderate sleep complaints	N=112	Health education		Tai Chi Chih (TCC)	Not specified	40 minutes	3	25 Weeks	PSQI	Significant ↓PSQI (↑Sleep Quality, ↑SE, ↑sleep duration, ↓sleep disturbances) in exercise group compared to control group
Herring et al., 2015[109]	Young women with Generalized Anxiety Disorder	N=30	Wait-list		Resistance exercise and dynamic cycling exercise	**Resistance=** 50% 1RM and progressing by 5% weekly; **Aerobic=** Not specified, but used HR and RPE	16 minutes	2	6 Weeks	PSQI, PSD	Compared to control, exercise groups showed significant: **Resistance=** ↓Weekend TIB, ↓weekend SOL, ↑Weekend SE; **Aerobic=** ↓Weekend TIB, ↓Weekend SOL; No significant changes in weeknight sleep outcomes for any group
Chen et al., 2016[110]	Nursing home older adults in wheelchairs	N=107	Maintained regular lifestyle	Participants randomized to one of three groups: a resistance training group, aerobic training group, or waitlist group	Wheelchair-bound Senior Elastic Band (WSEB) group-exercises	Not specified	40 minutes	3	12 Months	PSQI	Significant ↓PSQI in exercise group but not control group
Kline et al., 2011[97]	Sedentary overweight/obese adults with at least moderate-severity untreated OSA	N= 43	Stretching sessions 2x per week		Aerobic and resistance training	**Aerobic=** 60% HRR; **Resistance=** increased when 12 repetitions could be performed on the second set with proper form	**Aerobic=** 150 minutes per week of aerobic exercise + 5 minutes warm up + 5 minutes cool down; **Resistance=** 2 sets of 10-12 repetitions for 8 different exercises	4	12 Weeks	PSG, actigraphy, PSQI	Relative to controls, the exercise group showed significant changes in: **PSG:**↓AHI, ↓ODI; ↑%N3; **Actigraphy:**↓SOL, ↑SE, ↓sleep fragmentation; **PSQI:** ↓PSQI, ↓sleep quality, ↓SOL, ↓sleep disturbances; No significant change in body weight for either group
Servantes et al., 2011[112]	Chronic heart failure patients with sleep apnea	N=45	No training	Participants randomized to one of three groups: aerobic training, aerobic with strength training, or no training	Walking and strength training	**Aerobic=** Not specified, but monitored using HR; **Resistance=** 30-40% 1RM	**Aerobic=**Walking for 30-45 minutes + 10 minutes warm up + 10 minutes cool down; **Resistance=** Not specified	3 sessions in the first two months, and 4 sessions per week in the last month	3 Months	PSG	Both exercise groups showed significant changes in: ↓AHI, ↑SE compared to controls; No significant change in body weight for either group
Sengul et al., 2011[98]	Men with mild to moderate OSA	N= 20	No treatment		Breathing and low-moderate aerobic exercise	Submaximal intensity at 60–70% of VO2 max	1- 1.5 hours	3	12 Weeks	PSG, FOSQ, ESS	FOSQ, ESS scores, and AHI significantly improved in exercise group, but were not significantly different from the control group after 12 weeks. No change in BMI or other anthropometric measuresin post-intervention in either group
Herrick et al., 2014[113]	Institutionalized older adults with OSA	N= 144	Usual care	Participants randomized to one of three groups: exercise alone (N= 56), exercise in a group (N=41), or control (N= 47)	Resistance training and light walking	**Aerobic=** 2 metabolic equivalents per walking bout; **Resistance=** 86% of predicted 1RM	**Aerobic=**Walking for 5.87 ± 6.1 minutes/ bout; **Resistance=** Not specified	**Aerobic=** 2 days per week (1-3 bouts/ day); **Resistance=** 3 days per week	7 Weeks	PSG	Significant ↓AHI in exercise group compared to control group

Desplan et al., 2014[91]	Patients with mild to severe OSA	N=22	Education activity sessions	Exercise training was part of an inpatient rehabilitation program consisting of: individualized exercise training, education activity sessions, and dietary management	Warming up (15 min), cycle ergometer exercise training (45 min), muscle resistance training (30 min), stretching (15 min), and postural and balance exercises (15 min)	Not specified, but monitored using HR	2 hours	6	4 Weeks	PSG, OSLER, ESS, PSQI, Chalder Fatigue Scale	Relative to controls, the exercise group showed significant changes in: **PSG:** ↓AHI, ↓ ODI, ↓arousal threshold; **↓PSQI; OSLER:** no changes; **↓ESS; Chalder Fatigue Scale;** ↓physical fatigue, ↓mental fatigue; A significant ↓BMI, ↓neck circumference, ↓fat mass, ↓other anthropometric measures were found in the exercise group post-intervention but not the control group
Mendelson et al., 2016[114]	Coronary artery disease and central or obstructive sleep apnea	N=34	Usual activity level		Aerobic exercise training (Walking)	Moderate intensity (60% of VO2 max)	30 minutes walking (distance of approximately 1.6–2.0 km) + 10 minutes warm-up + 10 minutes cool down	5 Total: 3 supervised + 2 unsupervised	4 Weeks	PSG	Significant ↓AHI in exercise group compared to control group
Torres-Castro et al., 2019[116]	Patients with moderate to severe OSA	N=27	Received diet, sleep hygiene, and physical activity recommendations	Exercise training was part of a comprehensive community program consisting of: general physical activity, oropharyngeal exercises, and diet and sleep hygiene recommendations	Urban-walking program and oropharyngeal exercises	**Walking=** 60–80% of theoretical HR max; **Oropharyngeal exercises=** Not specified	30 minutes walking	3 walking sessions + 4 oropharyngeal exercises five days per week	8 Weeks	PSG, ESS	No significant difference in AHI post-intervention between groups; Significant reduction in AHI when considering only participants under the age of 60
Reid et al., 2010[123]	Sedentary adults with insomnia	N=17	Non-physical activity plus sleep hygiene education	Intervention involved aerobic exercise combined with sleep hygeine education	Moderate-intensity aerobic exercise	**During first 4-6 weeks=** Started at 55% HR max and increased by 5% per week ; **After first 4-6 weeks=** 75% of HR max	**During first 4-6 weeks=** Started at 10-15 minutes and increased by five minutes every week; **After first 4-6 weeks=** Two 20 minutes sessions or one 30–40 minute session	4	16 Weeks	PSQI, ESS	Compared to controls, the exercise group showed significant results in: **PSQI:** ↓PSQI, ↓SOL, ↑sleep duration, ↑SE, ↓daytime dysfunction; **↓ESS**
Afonso et al., 2012[124]	Post-menopausal women with insomnia diagnosis	N=44	No treatment	Participants randomized to one of three groups: control, passive stretching, or yoga	Yoga classes based on *yogasana* and Tibetan techniques	Not specified	1 hour	2	4 Months	PSG, ISI	Significant ↓ISI in exercise group compared to control group; No significant PSG difference between groups
Pinniger et al., 2013[160]	Individuals with self-reported depression and insomnia symptoms	N=64	Wait-list	Participants randomized to one of four groups: meditation, exercise, tango dance, or control	**Exercise group=** circuit training; **Tango group=** based on Argentinean close-embrace tradition	Not specified	1 hour class + 10 minute warm up	≈1 (6-8 sessions in the intervention total)	8 Weeks	ISI	Significant ↓ISI for Tango group compared to wait-list controls; No significant difference between ISI in exercise group and control group post-intervention
Irwin et al., 2014[121]	Older adults with chronic primary insomnia	N= 123	Sleep seminar education	Participants randomized to one of three groups: cognitive behavioural therapy, Tai ChiChih, or sleep seminar education (control)	Tai Chi Chih (TCC)	Not specified	2 hours	1	4 Months	PSG, PSQI	**PSG:** No significant differences in TCC and control; **PSQI:** TCC showed improvements in PSQI compared to control at months 4 (post-treatment) and 7(follow-up) (P values < 0.05), but not at month 16 (follow-up)
Hartescu et al., 2015[133]	Sedentary adults with insomnia	N=41	Wait-list with usual activity level	The exercise intervention started with a 4 week long conditioning period, in which participants engaged in moderate intensity physical activity in their own time, and then included the 30 minutes walking 5 times a week for the remainder of the intervention.	Moderate-intensity brisk-walking	Moderate according to NewLife NL-1000 activity monitor	30 minutes	5	6 Months	ISI, FSS	Significant ↓ISI in exercise group compared to control group; No significant FSS difference between groups
D'Aurea et al., 2019[123]	Patients with chronic insomnia	N=28	Non-intervention control	Participants randomized to one of three groups: resistance exercise, stretching, or control	Resistance exercise and stretching	**Resistance:** Started at an intensity of 50% 1RM and increasing to 60% after the second month; **Stretching** : Focused on the upper and lower limbs with 8-10 low-intensity stretches per body region.	**Resistance:** 50 minutes + 5 minutes warm up + 5 minutes cool down: **Stretching:** 45 minutes + 5 minute walk	3	4 Months	PSG, ISI, PSQI, actigraphy	Resistance and stretching groups significantly improved the following variables compared to control ↓ISI; **Actigraphy**: ↓SOL, ↓WASO, ↑SE; **PSQI:**↓PSQI,↑TST; No significant differences between resistance and stretching groups for actigraphy; No significant differences between all groups for PSG.

Table 1: RCTs examining the effects of chronic exercise on sleep parameters

1RM= One repetition maximum; HRR= Heart rate reserve; HR= Heart rate; RPE= Rate of perceived exertion; VO2 max= Maximal oxygen uptake;
PSQI= Pittsburgh Sleep Quality Index; PSG= Polysomnography; PSD= Pittsburgh Sleep Diary; FOSQ= Functional Outcomes of Sleep Questionnaire; ESS= Epworth Sleepiness Scale; OSLER= Oxford Sleep Resistance Test; ISI= Insomnia Severity Index; FSS= Fatigue Severity Scale;
TST= Total sleep time; SOL= Sleep onset latency; QOL= Quality of life; SE= Sleep efficiency; %N1/N2/N3= percent of total sleep time spent in N1/N2/N3; TIB= Time in bed; AHI= Apnea-hypopnea index; ODI= Oxygen desaturation index; WASO= Wake after sleep onset;
↓PSQI refers to a decrease in the global PSQI score; It is important to note that other measures may have been taken in these studies, but only sleep-related measures are reported here.

	Baseline Exercise Group	Baseline Relaxation Group	Post- 8 Weeks Exercise Group	Post- 8 Weeks Relaxation Group	Time		Condition		Time x Condition	
					p	F	p	F	p	F
ISI	17.38 ±5.15	16.88 ± 4.52	13.38 ± 3.66	15.00 ± 6.75	0.003	12.315	0.776	0.084	0.161	2.195
SE	75.43 ± 11.17	84.58 ± 14.62	76.01 ± 12.85	78.80 ± 10.40	0.451	0.601	0.269	1.322	0.359	0.898
HR at 50% ISO (bpm)	102.47 ± 11.44	106.56 ± 17.77	97.57 ± 9.71	107.59 ± 21.92	0.098	3.133	0.388	0.795	0.017	7.370
VO_2 Peak (mL/kg/min)	20.78 ± 6.38	20.21 ± 8.40	23.64 ± 5.47	19.41 ± 8.78	0.108	2.953	0.520	0.436	0.009	9.324
VO_2 Peak (L/min)	1.51 ± 0.43	2.05 ± 0.90	1.75 ± 0.50	1.97 ± 0.89	0.205	1.765	0.300	1.160	0.015	7.610
VO_2 at VT (mL/kg/min)	11.96 ± 3.19	12.79 ± 4.20	13.73 ± 2.97	12.66 ± 3.38	0.183	1.966	0.940	0.006	0.127	2.634
VO_2 at VT (L/min)	0.97 ± 0.32	1.24 ± 0.58	1.03 ± 0.31	1.32 ± 0.53	0.455	0.591	0.196	1.844	0.947	0.005
SOL (min)	15.31 ± 15.07	11.56 ± 7.03	21.50 ± 30.33	22.19 ± 19.52	0.068	3.927	0.867	0.029	0.609	0.274
WASO	87.56 ± 54.66	53.50 ± 57.91	85.25 ± 52.67	57.75 ± 33.56	0.955	0.003	0.125	2.657	0.848	0.038
SFI	12.48 ± 6.89	9.65 ± 2.34	13.48 ± 5.13	11.60 ± 4.19	0.230	1.575	0.294	1.187	0.691	0.164
TST (min)	354.38 ± 75.09	365.25 ± 70.87	342.44 ± 59.74	350.44 ± 59.74	0.527	0.421	0.710	0.145	0.945	0.005
Arousals (per hour)	117.73 ± 40.93	93.98 ± 26.03	134.98 ± 41.47	122.25 ± 20.21	0.027	6.114	0.213	1.703	0.559	0.358

Table 4: ANOVA results for all variables