

Physical activity, sedentary behaviour and cardiometabolic disease risk among adults living with obstructive sleep apnoea: Is there a case for exercise as an adjunct therapy?

By

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DECLARATION

I, Batsheva Channa Brand, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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"I can no other answer make, but, thanks, and thanks." -**William Shakespeare**

ABBREVIATIONS

AHI	Apnoea hypopnoea index
AT	Anaerobic threshold
BMI	Body mass index
CMD	Cardiometabolic disease
CON	Control group
CPAP	Continuous positive airway pressure
cpm	counts per minute
CRP	C-reactive protein
CVD	Cardiovascular disease
d	Day(s)
DBP	Diastolic blood pressure
EDS	Excessive daytime sleepiness
ESS	Epworth Sleepiness Scale
FEV	Forced expiratory volume
FOSQ	Functional Outcomes of Sleep Questionnaire
FVC	Forced vital capacity
GERD	Gastroesophageal reflux disease
h	Hour(s)
HIIT	High intensity interval training

HR	Heart rate
HRQOL	Health related quality of life
HRR	Heart rate reserve
LRchi²	Likelihood ratio chi-square test
MAP	Mean arterial pressure
MET	Metabolic equivalent
min	Minute(s)
MPA	Moderate intensity physical activity
MVPA	Moderate to vigorous intensity physical activity
n	Number
NCD	Non-communicable disease
NEAT	Non-exercise activity thermogenesis
ODI	Oxygen desaturation index
OSA	Obstructive sleep apnoea
PAP	Positive airway pressure
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSG	Polysomnography (sleep study)
PSQI	Pittsburgh Sleep Quality Index
RCT	Randomized control trial
RPE	Rating of perceived exertion
SB	Sedentary behaviour

SBP	Systolic blood pressure
SD	Standard deviation
SES	Socio-economic status
SNS	Sympathetic nervous system
SpO₂	Oxygen saturation
T2DM	Type II diabetes mellitus
VO₂	Volume of oxygen consumption
VPA	Vigorous intensity physical activity
Y	Year(s)
WC	Waist circumference
WHO	World Health Organization
wk	Week(s)
1RM	One-repetition maximum

ABSTRACT

BACKGROUND

Sleep disorders, and resultant poor sleep quality, have emerged as risk factors for cardiometabolic disease (CMD), including obesity, hypertension, type II diabetes mellitus (T2DM), and cardiovascular disease (CVD). Obstructive sleep apnoea (OSA) is the second most common sleep disorder and is characterized by multiple obstructive apnoea episodes (i.e., cessation of breathing due to complete collapse and occlusion of the upper airways), hypopnoea events (i.e., partial collapse and occlusion of the upper airways) and respiratory effort-related arousals during sleep. Not only is sleep therefore fragmented in untreated OSA, but patients also present with excessive daytime sleepiness and dysfunction. Sleep fragmentation in itself has been shown to be associated with metabolic dysfunction, possibly through elevated sympathetic nervous system (SNS) output. Therefore, it is unsurprising that OSA is also associated with many adverse cardiometabolic health outcomes, with epidemiological research showing specific associations with cardiovascular mortality, stroke, coronary artery disease, diabetes, and obesity in particular. Increased inspiratory efforts against a closed airway during an apnoea episode creates extreme negative intrathoracic pressures, elevated venous return and overload of the right ventricle resulting from recurrent pressure fluctuations, while the subsequent hypoxia and hypercapnia result in increased SNS outflow. As hypoxias and sleep fragmentation have each been shown to elevate SNS tone, OSA is hence characterized by elevated SNS output as one of the condition's pathogenetic sequelae. Given the effects of SNS tone on blood pressure, inflammation, and insulin sensitivity, these factors represent an important common pathway mediating the cardiometabolic effects of untreated OSA.

The current gold-standard treatment for moderate and severe OSA is continuous positive airway pressure (CPAP) therapy. While effective, CPAP therapy has limitations related to compliance and cost. Surgical interventions are also considered in some cases in which anatomical abnormalities are thought to cause the obstructive events during sleep which typify OSA. By the time most patients are diagnosed, and treatment is begun for OSA, they also usually present with many comorbidities. Patients with OSA often have comorbidities that necessitate addressing their weight, making weight loss a recommended part of their management protocol. There is evidence to suggest that weight loss in OSA sufferers contributes to a reduction in the severity of OSA and risk for comorbidities, potentially in part

through altering inflammatory pathways associated with obesity. Weight loss is usually addressed through dietary interventions, but more recently the role of exercise in this regard has been investigated.

Physical activity in persons with OSA is thought to play a protective role in the course of the disease by means of multiple mechanisms including: preventing a decline in night time cardiac autonomic nervous system function, increased oxygen consumption, reducing both the apnoea hypopnea index (AHI) severity and excessive daytime sleepiness, reduction in body weight, body mass index (BMI) and adipose tissue in the upper respiratory tract and pharyngeal region, reduction in the CVD risk factors associated with inflammation, thereby, leading to an improved quality of life. The additional benefits of physical activity related to mood comprise reduced levels of anger, depression, bodily pain, and total mood disturbances, and increased participation in social activities. Thus, there appears to be a place for adjunct therapies, such as exercise and dietary support, to complement standard treatment approaches.

Given the promising evidence for the role of exercise as an adjunct therapy for OSA patients, we would like to design and implement an exercise intervention, ultimately for use in the public healthcare setting in South Africa where access to CPAP therapy is constrained. Therefore, the purpose of this thesis is to understand whether there is a need for exercise as an adjunct therapy for adults being treated for OSA and if so, what forms of activity are most likely to be effective in managing comorbidity risk. Accordingly, the aims of this thesis are:

Aim 1: To characterise and compare the sleep, physical activity and CMD risk profiles of adults living with OSA and being treated with CPAP therapy (OSA group) to age- and gender-matched adults without OSA (CON group).

Aim 2: To systematically review the nature and efficacy of exercise interventions in reducing OSA severity and CMD risk factors in adults with OSA.

METHODS

To address Aim 1, a cross-sectional observational study was conducted on 37 participants recruited into one of two age- and gender-matched groups: the OSA group comprised adult men and women ($n=18$), who were previously diagnosed with moderate to severe OSA ($AHI \geq 15$) but are now on CPAP therapy, and the CON group comprised adult men and women ($n=19$) with no previous diagnosis of OSA, nor symptoms or signs of OSA. All participants provided written informed consent, completed a detailed questionnaire capturing demographic data, medical history, past and present habitual physical activity habits, sleep habits, and quality of life information. The investigator measured their weight, height, waist circumference (WC), neck circumference, and resting blood pressure and heart rate (HR). Participants were then given a small wrist-worn accelerometer to wear for the subsequent seven days to measure their habitual sleep, physical activity, and sedentary behaviour (SB). They simultaneously completed a sleep and physical activity diary.

To address Aim 2, a systematic review was conducted according to the PRISMA guidelines across three electronic databases: PubMed, Scopus, and ISI Web of Science, up until 1 January 2023. Original peer-reviewed research studies reporting on the efficacy of exercise interventions in OSA patients and control groups were considered for inclusion in the present review. Studies were excluded if they reported on central sleep apnoea, did not use an experimental trial design, or did not report on AHI, measures of fitness, body composition or sleep outcomes.

Original peer-reviewed research studies reporting on the efficacy of exercise interventions in OSA patients were considered for inclusion in the present review. Studies were included if they: (1) were original research studies, (2) used an experimental trial design (e.g., randomized controlled trial, observational or prospective cohort study), (3) had a sample of human adult participants (i.e. aged 18 years or older), (4) included both OSA participants (diagnosed $AHI \geq 5$) and controls ($AHI < 5$), (5) tested an exercise intervention, (6) reported on pre and post measures for AHI and measure of fitness (e.g. VO_2 peak) or body composition (e.g. BMI) or sleep (e.g. Epworth Sleepiness Scale score) and (7) were published in English. Studies were excluded if they (1) reported on patients with central sleep apnoea or (2) were conference abstracts, other published abstracts, and grey literature (e.g., reports, white papers, academic theses, or dissertations).

RESULTS AND DISCUSSION

The main finding of the observational study (Aim 1) indicated that compared to the CON group (age: 56 (50-63) years, 21% women), the OSA participants (age: 59 (49-62) years, 22% women) spend proportionally more time every day in sedentary behaviour (OSA: 70.12±11.14%, CON: 61.94±10.65%, $p=0.029$) and relatively less time in moderate (OSA: 11.59±4.95%, CON: 15.68±5.02%, $p=0.017$) and vigorous (OSA: 3.81[1.64-6.08]%, CON: 6.05[4.27-9.47], $p=0.042$) physical activity. From a descriptive perspective, the OSA group had a higher BMI ($p<0.001$), neck circumference ($p<0.001$), WC ($p<0.001$), systolic blood pressure (SBP) ($p=0.039$), total number of chronic conditions ($p=0.007$), daytime sleepiness ($p=0.007$) and later wake-up times ($p=0.035$) compared to the CON group, but self-reported health scores were not different between the groups. An interaction effect between group and diary-derived weekly physical activity time indicated that for every additional diary-derived minute of physical activity per week, the OSA group were more likely to have hypertension compared to the CON group.

The present systematic review (Aim 2) indicated that, of the 10 included studies, eight observed significant reductions in AHI in patients with OSA in response to an exercise intervention (seven without CPAP therapy). While five of the studies which observed reductions in AHI, also demonstrated improvements in markers of cardiorespiratory fitness, only one was accompanied by improvements in BMI and neck circumference. Furthermore, exercise interventions combining both aerobic and resistance training were more effective in improving AHI than resistance training alone. With regards to duration, while positive changes were observed in as little as one month and sustained for as long as nine months, it seems that at least three exercise sessions per week are required. However, if fewer sessions are to be prescribed, exercise intensity needs to be high, and walking alone may not be sufficient to induce changes in AHI.

CONCLUSION

The observational study concluded that individuals with OSA are less physically active and have more abdominal obesity than age matched adults who do not suffer from OSA. Not only might it be beneficial for OSA patients to reduce sedentary time, but there is a case for them

to include more vigorous intensity physical activity in their daily lives. In fact, OSA individuals who become more vigorously physically active might be expected to have the same positive responses on adiposity compared to adults without OSA. However, there was no interaction effect meaning that OSA individuals who become more vigorously physically active should respond the same as the CON group in having the same chance of reducing BMI, WC, while also improving cardiorespiratory fitness and blood pressure control. However, the group effect suggested that regardless of SB or physical activity, BMI is still higher in the OSA group and therefore the exact effects exercise may have on weight control remain unclear. The group effect suggested that regardless of SB or physical activity, BMI is still higher in the OSA group. Furthermore, having diagnosed comorbidities was not associated with SB or physical activity levels so having other conditions neither limited physical activity nor increased SB. When accounting for SB, the OSA group was more likely to have another condition, hence reducing SB may have a favourable effect on associated comorbidities. In addition, the OSA group, who spent more time being active, were less likely to have hypertension, contrary to the CON group who was less active, was more likely to have hypertension. When accounting for SB, moderate physical activity, and diary-derived physical activity time, the OSA group was more likely to have diabetes. Lastly, despite the similar sleep characteristics between the groups, the OSA group still had excessive daytime sleepiness.

Based on the systematic review, while relatively few robust studies have investigated the efficacy of exercise interventions in OSA patients, 80% demonstrated efficacy in improving AHI (a marker of OSA severity). Since 63% showed accompanying improvements of cardiorespiratory fitness parameters, but only 13% improved BMI, a marker of obesity, the efficacy of exercise interventions on OSA severity may be more related to changes in the cardiorespiratory system than body composition. Exercise programmes that combine aerobic and resistance training and include at least two exercise sessions per week of at least 30 minutes each, with aerobic training being at moderate to high intensity are most likely to be effective. Of concern is that very little impact of the exercise interventions on obesity, a major risk factor for OSA and its associated comorbidities, was observed, suggesting that exercise interventions may well need to accompany dietary strategies targeted at weight loss.

This thesis provides evidence on the importance of healthy lifestyles (particularly more physical activity at higher intensities and less sedentary time) in the prevention and treatment of OSA and its comorbid conditions. Furthermore, this thesis showed recommendations for the importance of exercise as an adjunct therapy to CPAP, specifically in the South African

cohort, where the socio-economic conditions restrict the availability of treatment modalities for OSA sufferers.

CHAPTER 1: INTRODUCTION

1.1 INTRODUCTION AND SCOPE OF THE THESIS

Sleep is essential for recovery, supports normal brain function and ensures optimum physical and mental health (Vyazovskiy, 2015). Chronic disturbances in sleep have far reaching health implications. In general, poor sleep quality has been associated with both short- and long-term negative health outcomes such as increased risk for cardiometabolic disease (CMD) including obesity, hypertension, metabolic syndrome, dyslipidaemia, type II diabetes mellitus (T2DM), and cardiovascular disease (CVD), as well as mood-related disorders (Medic, Wille, & Hemels, 2017). Sleep can be disturbed by sleep disorders, such as insomnia, the most common sleep disorder and obstructive sleep apnoea (OSA), the second most common sleep disorder (Ong & Crawford, 2013) and the focus of this dissertation. Individuals who suffer from untreated OSA experience highly disturbed and non-restorative sleep, with negative consequences in their daytime functioning and quality of life.

1.2 OBSTRUCTIVE SLEEP APNOEA

1.2.1 Definition, classification, and pathophysiology of obstructive sleep apnoea

OSA can be defined as a sleep-related breathing disorder whereby obstruction of the upper airway during sleep (Figure 1.1) causes multiple episodes of absent or reduced ventilation through restricted air flow despite active respiratory muscles. Major determinants of upper airway patency during sleep are related to the anatomy of the upper airway, especially its size or diameter, which in turn is determined by soft-tissue and skeletal factors (Strollo et al. 2014). These may differ in individuals with different body weights and shapes. In obese patients, increased adipose tissue in the neck may predispose the airway to narrowing or collapse, especially when the patient is in the supine position (Beatty et al. 2021). Patients of normal body weight who develop sleep apnoea may have other anatomical features such as tonsillar hypertrophy or craniofacial skeletal abnormalities that may predispose the airway to narrowing or closure during sleep (Dempsey, Veasey, Morgan, & O'Donnell, 2010).

OSA is clinically diagnosed using an overnight polysomnography (PSG) sleep study. Some studies include the assessment of multiple physiological and respiratory parameters such as abdominal and thoracic breathing, nasal airflow, oxygen saturation and heart rate (HR). Strict criteria based on sleep scoring guidelines published by the American Academy of Sleep Medicine are applied when scoring the PSG for diagnostic purposes (Collop et al. 2007). The resultant Apnoea Hypopnoea Index (AHI) is used to determine the severity of OSA and reflects the number of both apnoeic (complete reduction in airflow) and/or hypopnoeic (partial reduction in airflow) events occurring per hour of sleep. Mild OSA is defined as an AHI score between 5 but less than 15 events per hour, moderate OSA between 15 but less than 30, and severe OSA with a score ≥ 30 events per hour (Chen et al. 2023).

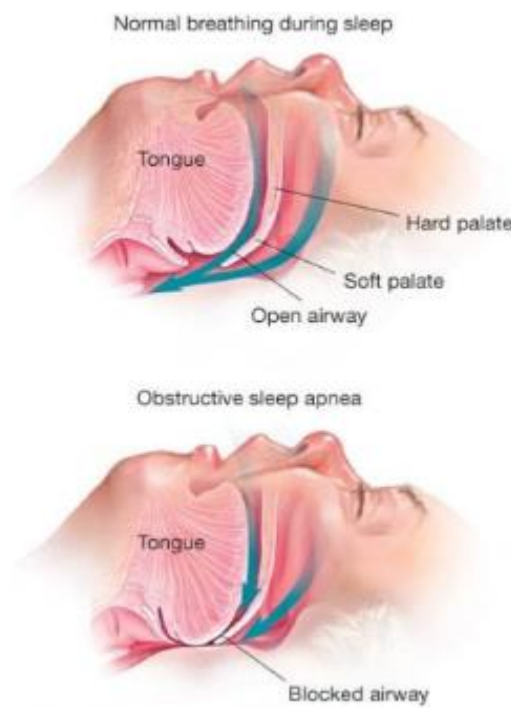


Figure1.1: Diagram to illustrate normal passage of air through the upper airways during sleep (upper image) and occlusion of the upper airways during sleep experienced by individuals with obstructive sleep apnoea (lower image). “Used with permission of the Mayo Foundation for medical education and research, all rights reserved.”

1.2.2 Obstructive sleep apnoea prevalence and risk factors

The overall global population prevalence of OSA (i.e., AHI ≥ 5 events/hour) ranges from 9% to 38% and is higher in men, older individuals and in people with obesity (Jennum & Riha, 2009; Senaratna et al. 2017; Tudor-Locke et al. 2004). Of interest is that the predominance of OSA

in men is well-documented in Western and Asian populations, particularly in Europe, the USA, and China. Given that there is limited information regarding its prevalence among men of African ancestry, there is a need for more research in these populations to better understand the condition across diverse ethnic groups (Bentley, Callier, & Rotimi, 2020). The prevalence of moderate and severe OSA (AHI ≥ 15) in the general adult population ranges from 6% to 17% and can be as high as 49% in older age groups (Jennum & Riha, 2009; Senaratna et al. 2017). In some elderly groups, the prevalence can be as high as 90% in men and 78% in women (Senaratna et al. 2017). Obesity is also considered a risk factor for OSA with one study reporting that OSA was diagnosed in 63% of obese individuals (BMI $\geq 30\text{kg/m}^2$) (Tudor-Locke et al. 2004). There are currently limited published OSA prevalence data for the South African population, however, one study has observed a prevalence of 29% among older South African adults living in a rural, low-income setting (Roche, 2021).

Based on a recent systematic review assessing risk factors for OSA, some of the factors identified as risk for the development of OSA; age >35 , BMI >25 , diabetes, hypercholesterolemia, hypertension, alcoholism. There is however an increased risk with a bidirectional association between OSA and its associated cardiometabolic risk factors (Geovanini et al. 2018).

1.2.3 Consequences of untreated obstructive sleep apnoea

There is substantial evidence to suggest that individuals with OSA experience poor health, which can impact quality of life. For example, Pinto et al. (2016) evaluated 100 individuals with OSA (84 men, 16 women, mean age of 50 years) and observed that two thirds of the patients had comorbidities: hypertension (39%), obesity (34%), depression (19%), gastroesophageal reflux disease (GERD, 18%), T2DM (15%), hypercholesterolemia (10%) and asthma (4%). Furthermore, since comorbidities were reported in 56% of patients diagnosed with mild OSA, 68% with moderate OSA, and 70% of patients with severe OSA, a greater predisposition to comorbidities is associated more severe OSA (Pinto, Ribeiro, Cavallini, Duarte, & Freitas, 2016). In addition to these cardiopulmonary and endocrine comorbidities, individuals with OSA are also more likely to experience more cognitive impairment (Stavrou et al. 2021), excessive daytime sleepiness, work-place errors, traffic accidents and mood disorders (Stavrou et al. 2021). These health and societal consequences may result in significant economic burden, making identification and treatment of sleep apnoea critical.

Previous studies have shown strong associations between OSA and hypertension, coronary artery disease, arrhythmias, heart failure, and stroke (Devulapally, Pongonis, & Khayat, 2009). In randomised trials, treating OSA with continuous positive airways pressure therapy (CPAP) lowered blood pressure and, in patients with heart failure, improved cardiac function. Current data therefore suggest that OSA increases the risk of developing cardiovascular disease (CVD), and that its treatment has the potential to diminish such risk (Bradley & Floras, 2009). The relationship between obesity, CVD and OSA is complex. It was previously assumed that the consequences of CVD sequelae and OSA imply a relationship between obesity and CVD. Recent data suggest that OSA is independently associated with CVD risk factors that comprise metabolic syndrome, including hypertension, insulin resistance, and impaired glucose tolerance. While an increased BMI contributes to CVD risk, the pathogenic pathways within OSA are likely related to multiple pathways including hypoxia and increased chronic inflammation, to name a few. Hence, this may result in OSA also being independently associated with an increase in the cardiovascular risk factors that comprise the metabolic syndrome and its overall prevalence and thus help explain the increased cardiovascular morbidity and mortality associated with this condition (Coughlin, Mawdsley, Mugarza, Calverley, & Wilding, 2004).

One such pathway related to the relationship whereby OSA is understood to alter glucose metabolism and promote insulin resistance is associated with an increased risk of T2DM (Mitra, Bhuiyan, & Jones, 2021). Furthermore the fact that obesity is a risk factor common to people with OSA and diabetes is important since metabolic disorders including T2DM, lipid profile derangements, and non-alcoholic fatty liver disease may also stem from OSA (Strausz et al. 2018). Doumit et al. (2016) indicated that OSA has been shown to increase the risk and severity of T2DM independent of age and obesity, which is notable because age and obesity are risk factors for both OSA and T2DM.

Inflammatory cytokines, which when elevated and sustained can be predictive for obesity and T2DM (Ellulu, Patimah, Khaza'ai, Rahmat, & Abed, 2017). This would support the notion that the presence of greater visceral adiposity increases the risk of impaired glucose tolerance and furthermore impacting its relationship with OSA. It has been well established that obesity, particularly abdominal obesity (i.e., waist circumference), is significantly associated with increases in systemic inflammation. Visceral fat promotes systemic inflammation by secreting inflammatory adipokines into the portal circulation which drains visceral fat (Ellulu et al. 2017).

Thus, abdominal fat enhances local inflammation and is one of the mechanisms thought to be associated with increased CMD risk.

OSA itself causes episodes of chronic intermittent hypoxia which increase not only sympathetic nervous system (SNS) activity, but also increase oxidative stress which further increase underlying inflammatory processes. These factors likely also contribute to the cardiometabolic consequences of OSA (Sforza et al. 2016).

This association between OSA with a systemic inflammatory response, resulting in atherosclerosis, insulin resistance, type II diabetes, and lipid profile changes, greatly increases morbidity and mortality in patients with untreated OSA (F. M. D. d. Andrade & R. P. Pedrosa, 2016). Furthermore, increased numbers of severe cardiovascular and cerebrovascular events are also seen in untreated OSA individuals. These include myocardial infarction, heart failure, stroke, and sudden cardiac death (Berger et al. 2019). It has also been well-established that individuals who are less physically active are more likely to have higher systemic inflammation (Conte et al. 2020). It is hence evident that the pathogenesis and sequelae of OSA are multifactorial and multifaceted adding to the complexity and variable presentations and associated comorbid conditions.

1.2.4 Treatment and management of obstructive sleep apnoea

Due to the multifactorial nature of OSA, there are several treatment modalities that may be considered, some in combination, depending on the clinical presentation of the individual. Treatment options include CPAP therapy, surgical intervention, mandibular adjustments, orthodontic devices, and lifestyle adaptations such as changes to diet and physical activity. According to the American Academy of Sleep Medicine, CPAP should ideally be the first-line treatment for moderate to severe OSA (AHI ≥ 15 events/h) and is considered the current gold standard of treatment for the condition unless surgical intervention is warranted. The clinical decision to prescribe CPAP is based on the likelihood of symptom relief and cardiovascular protection (F. M. D. d. Andrade & R. P. Pedrosa, 2016). Patients are also assessed as to whether anatomical structures related to the upper airway can be improved with either an oral appliance or surgical procedure to enhance outcomes. Examples of surgical procedures commonly used to address OSA include an upper airway bypass such as a tracheostomy, upper airway reconstruction, uvulopalatopharyngoplasty, genioglossal advancement and maxillomandibular surgical advancement (Mehra & Wolford, 2000).

Addressing any associated underlying medical conditions that may contribute to OSA risk and associated comorbidities (e.g., elevated BMI) is important. Therefore other forms of conservative treatment for OSA include behavioural changes targeted at weight loss (e.g. increased physical activity, reduced caloric intake), avoidance of alcohol and sedatives (i.e. substances which may promote upper airway collapse during sleep), optimization of nocturnal positioning (to minimise upper airway collapse and laryngopharyngeal reflux also called extra-oesophageal reflux) and avoidance of short sleep, which will only exacerbate the sleep deprivation effects already experienced by OSA patients (Abad & Guilleminault, 2003).

Given that many patients with OSA are obese and suffer from lifestyle-related comorbidities, they are often advised to manage their weight with dietary changes as part of their treatment plan. It has been reported globally that compliance to CPAP therapy is poor (Aalaei et al. 2020). Furthermore, in South Africa for example, CPAP therapy is often inaccessible to large parts of the population who are of low socio-economic status (SES), reliant on public health care systems with limited resources. It is therefore imperative to explore adjunct therapies for OSA, particularly in countries like South Africa where CPAP treatment is unaffordable, and the same may apply to surgical treatments. There is, however, evidence to suggest that a dual approach to managing weight, i.e., reducing caloric intake and an increase in physical activity, together, are effective in this regard (Avenell et al. 2004).

Furthermore, it has been shown that adults who report low sleep quality also present with lower levels of physical activity compared to adults without disrupted sleep (Kline, 2014). Sleep disruption is a hallmark characteristic of OSA, and there are data to suggest a reduced prevalence and incidence of OSA in those who exercise regularly (Kline, 2014). An added benefit to addressing physical activity in patients with OSA may be an important therapeutic approach. The low levels of physical activity observed in OSA patients have been attributed to the fatigue, excess weight, and low energy that characterize the clinical presentation of OSA (Monique Mendelson et al. 2018). Exercise may provide the benefits of addressing both weight loss and inflammation in OSA patients, as well as lowering the risk of cardiovascular disease (CVD), depression, and comorbidities that arise from obesity.

The role of lifestyle interventions as an adjunct therapy to manage OSA severity has, until relatively recently, received little attention in the literature. Two studies provide evidence for the efficacy of combined dietary and exercise programmes for reducing OSA severity (D. A. Dobrosielski, Patil, Schwartz, Bandeen-Roche, & Stewart, 2015; Norman, Von Essen, Fuchs, & McElligott, 2000). In addition to, and independent of weight loss, regular physical exercise has been proposed to increase upper airway dilator muscle tone, reduce fluid accumulation in the neck, reduce the systemic inflammatory response, increase slow-wave sleep time, reduce daytime sleepiness, increase sleep efficiency and maximize oxygen consumption in OSA patients (F. M. Andrade & R. P. Pedrosa, 2016).

While the mainstay treatment for OSA usually refers to the use of CPAP, from the associations above including the well-established finding that individuals who are less physically active are more likely to have higher systemic inflammation (Conte et al. 2020), it becomes clearer why increased physical activity may greatly contribute to the improved long-term wellbeing of these patients by aiding the maintenance of or decrease in weight, improvement of metabolic profiles and cardiovascular parameters such as blood pressure. Additionally, increased arousals increase sympathetic activity increasing blood pressure, causing CVD.

1.3 PHYSICAL ACTIVITY

1.3.1 Physical activity and sedentary behaviours

Physical activity is defined as “any bodily movement produced by the skeletal muscles that results in increased energy expenditure” (Caspersen, Powell, & Christenson, 1985) and is currently seen as one of the most powerful health-promoting behaviours, especially in aiding the management of body weight. Physical activity is a multi-faceted behaviour comprising of several components: frequency, intensity, type, and time. ‘Frequency’ relates to how often the activity is performed. ‘Intensity’ relates to how hard the activity is performed, which can depend on the ‘type’ of activity. Lastly, ‘time’ refers to the duration of one session of activity. Sedentary behaviour, on the other hand, is defined as “any waking behaviour characterized by an energy expenditure ≤ 1.5 METs (metabolic equivalent) while in a sitting, reclining or lying posture” (Barnes et al. 2012). Physical activity at a moderate intensity and vigorous intensity are classified as an energy expenditure of 3-6 METs and >6 METs respectively (American College of Sports, Riebe, Ehrman, Liguori, & Magal, 2018)

Exercise training is a “subset of physical activity that is planned, structured, and repetitive” (Caspersen et al. 1985). Exercise modes can be divided into two categories: physical training, comprising aerobic and strength work, and motor training, comprising balance, coordination, and flexibility. Current recommendations for physical activity in adults are as follows: accumulate either at least 150–300 minutes per week of moderate-intensity, 75–150 minutes per week of vigorous-intensity aerobic physical activity, or an equivalent combination of moderate- and vigorous-intensity aerobic activity, which must include 60 minutes or more of daily physical activity, resistance training and bone strengthening exercise preferably done at least three days per week (Y. J. Yang, 2019).

1.3.2. Benefits of physical activity

The benefits of physical activity have been well demonstrated as have the negative consequences of sedentary behaviour on physical and mental wellbeing (Macfarlane, Lee, Ho, Chan, & Chan, 2006; Reilly et al. 2008). Physical activity has thus become an increasingly prominent intervention tool in overall health management serving in the primary and secondary prevention of many non-communicable disease processes. The most important benefits include a reduction in CVD, obesity, depression, and premature death (Booth, Roberts, & Laye, 2012). The physiological mechanisms that underlie these benefits occur at both a cellular and multisystem level (Neufer et al. 2015). It has also been shown that prolonged periods of occupational or leisure-time sitting have adverse health effects independent of exercise performed before or after.

Importantly, not all forms of exercise are equal, each affecting the body in different ways with varying effects on, weight, CVD risk, mental health. In a study by Joseph et al. 2019 levels of physical activity were found to have the same effect on outcome independent of the level of blood pressure (Joseph et al. 2019). Thus, recommendations on physical activity should not be modified by the level of blood pressure but should be the same in all blood pressure-levels to achieve maximum health benefits. Further, the association between physical activity and outcome in stage 2 hypertension (blood pressure >160/100 mm Hg) is the same as in the other blood pressure groups. This is an important finding since precautions in recommending physical activity in patients with stage 2 hypertension. According to the European Society of Cardiology/European Society of Hypertension guidelines 2018, physical activity is not recommended in persons with blood pressure >180/110 mm Hg (Williams et al. 2018). Even in stage 2 hypertension and in patients with blood pressure >180/110mmHg, the highest level of physical activity is associated with lower mortality and better cardiovascular outcomes

compared to both inactivity and light activity, suggesting no dangerous effects of exercise in this patient group.

Almost any form of physical activity is beneficial, whether part of a regular exercise programme or as a series of intermittent, incidental, non-purposeful, lifestyle-embedded activities that result in non-exercise activity thermogenesis. Furthermore, the health benefits of exercise appear to be dose-dependent (Miller et al. 2016).

1.3.3. Measuring physical activity

Common clinical methods used to measure and assess physical activity include HR monitoring, questionnaires, accelerometers, and pedometers (Sylvia, Bernstein, Hubbard, Keating, & Anderson, 2014). HR monitors indirectly measure the intensity of physical activity. On their own they do not provide information on the type of activity being performed but can easily be used in combination with an activity diary to gain this additional information when needed. Accelerometers are small light-weight devices typically worn on the hip and wrist, and provide information on the duration, frequency, time, and intensity of physical activities based on movement (Sylvia et al. 2014). They do not, however, give information on the type of activity being performed. Pedometers in turn count total steps taken, thereby measuring distance covered through movement. Questionnaires are simple, affordable, easy to administer, often don't take long to complete, can include duration and frequency of habitual physical activity patterns, and are frequently used in public health settings and in large-scale research. Since they are subjective, unfortunately the accuracy of questionnaires and surveys often falls victim to recall bias (Sylvia et al. 2014). Thus, since each method has its own advantages and limitations, combining several methods of measurement can provide a more accurate representation of physical activity levels.

1.3.4 Consequences of physical inactivity and excessive sedentary behaviour

Recent evidence suggests that sedentary behaviour (SB) is independently associated with traditional CVD risk factors and increased CVD morbidity and global mortality, regardless of physical activity volume (Young et al. 2016). Being inactive contributes significantly to unhealthy weight gain and obesity, high cholesterol, and elevated blood glucose levels, all of which increase the risk of developing CMD (WHO 2010). It has also been shown that physically active adults are at a reduced risk of all-cause and CVD mortality, breast and prostate cancer, fractures, recurrent falls, functional limitation and cognitive decline, dementia, Alzheimer's disease, and depression, as well as further experiencing healthier ageing trajectories with better quality of life and improved cognitive functioning compared to their less

active peers (Cunningham, R, Caserotti, & Tully, 2020). Furthermore, physical activity helps prevent weight gain, reduces the risk of many chronic diseases, such as heart disease, cancer, and type II diabetes, helps reduce feelings of anxiety and improves sleep quality, improves cognitive ability, reduces the risk of dementia, and improves bone and musculoskeletal health (Cunningham et al. 2020).

1.4 PHYSICAL ACTIVITY AND CARDIOMETABOLIC DISEASE RISK IN INDIVIDUALS WITH OBSTRUCTIVE SLEEP APNOEA

1.4.1 The interplay between physical activity levels, sedentary behaviour and cardiometabolic disease risk in individuals with obstructive sleep apnoea

Based on a recent systematic review and meta-analysis, OSA sufferers typically present with low levels of objectively measured physical activity when compared with public health physical activity guidelines (as mentioned above) (Monique Mendelson et al. 2018). In adults, physical activity is inversely associated with low-grade inflammation (Wärnberg, Cunningham, Romeo, & Marcos, 2010) and since OSA is viewed in part as an inflammatory disease, this may be one of the mechanisms by which physical inactivity contributes to CMD risk in OSA sufferers. Obesity may be an additional contributing factor to OSA severity, as the mean BMI of the OSA sufferers included in the meta-analysis was over 30 kg/m² for six out of the eight studies included, indicating that most individuals with OSA were obese. Obesity in itself may have contributed to the low levels of physical activity observed in the OSA population or vice versa. A recent study examining physical activity levels in OSA sufferers with varying levels of obesity, found that physical activity levels tended to be lower with increasing obesity (DeLany, Kelley, Hames, Jakicic, & Goodpaster, 2013). Furthermore, OSA sufferers with obesity accumulated on average $6,617 \pm 2,673$ steps per day, which was not only far lower than the recommended threshold of 10,000 steps per day, (Vorvolakos et al. 2020), but was significantly lower than the physical activity levels achieved in lean participants with OSA ($9,951 \pm 3,487$ steps per day) OSA. Thus, in OSA sufferers, the same relationship between obesity and physical activity holds true as for the general population – i.e., less physical activity results in higher risk for obesity and hence is important since (i) obesity risk factor for CMD disease - which is prevalent as a comorbidity on OSA sufferers.

BMI and obesity were also positively correlated with AHI and hence OSA severity (Pinto et al. 2016). As previously mentioned, obesity and its related comorbidities are thought to be associated with underlying chronic inflammatory processes, and as OSA is viewed in part as an inflammatory disease, it may be yet another of the mechanisms by which obesity and lack of physical activity contribute to CMD risk in individuals with OSA (Jehan et al. 2017).

1.4.2 Benefits of addressing low physical activity in individuals with obstructive sleep apnoea

The literature has extensively described the protective capacity of physical activity on CMD development. Increased physical activity is associated with optimum glucose metabolism, body composition, blood pressure, inflammatory profile, reduced fat accumulation in the cervical region, improved respiratory muscle strength, decreased overnight fluid shift from the legs to the pharynx wall, and increased life expectancy (Myers et al. 2015; Norman et al. 2000; Stefania Redolfi et al. 2015; Schwartz, Gold, Schubert, & Stryzak, 1991). Given the unfavourable cardiometabolic profile found in individuals with OSA, increased physical activity could be considered an adjunctive tool in the treatment of OSA (Devon A Dobrosielski, Papandreou, Patil, & Salas-Salvadó, 2017).

More recent studies have focused on exercise programmes for the OSA population as they constitute a low-cost, easy-to-use treatment modality and have been shown to be effective in mitigating several harmful consequences of OSA, including cardiovascular disorders, glucose intolerance, and fatigue (F. M. D. d. Andrade & R. P. Pedrosa, 2016).

1.4.3 Making a case for physical activity as an adjunct therapy for individuals with obstructive sleep apnoea

In view of all of these proposed benefits, improving physical activity levels should be considered as a key component in the management of individuals with OSA. Increasing physical activity levels, with structured exercise training programmes for instance, has the potential to reduce OSA severity and may also reduce important CMD risk factors associated with OSA (Monique Mendelson et al. 2018). CPAP alone is limited in its effectiveness, however physical activity as an adjunct therapy may improve quality of life in symptomatic OSA sufferers. Hence, there is a strong need for a combined treatment approach for individuals with OSA with the aim of optimizing and controlling risk factors and reducing long-

term morbimortality. Nevertheless, more research is needed to further clarify the potential therapeutic role of exercise in the management and treatment of OSA.

While there is some evidence that the OSA population is less active than the general population (Lee, Nagubadi, Kryger, & Mokhlesi, 2008), whether this relates to sedentary behaviour or intensity of physical activity has not been well-described. A systematic review by Bollens et al. (2018) examined the efficacy of exercise as a treatment modality for OSA patients, but which specific components of an exercise intervention (mode, frequency, intensity, and duration) yielded the best results, has yet to be examined. Thus, there is currently no consensus on how exercise is best prescribed for OSA sufferers. Identifying which factors (mode, frequency, intensity, and duration) are important in determining the success of an exercise intervention for OSA patients will help guide the development of future exercise programmes for people living OSA.

1.5 PURPOSE OF THIS THESIS

Accordingly, the aims of this thesis are:

Aim 1: To characterise and compare the CMD risk, physical activity and sleep profiles of adults living with OSA (OSA group) and being treated with CPAP therapy to age- and gender-matched adults without OSA (CON group).

Objective 1: To characterise the CMD risk profile of both groups utilising medical history questionnaires (diagnosed chronic conditions and medication use), anthropometry (BMI, waist circumference, neck circumference) and physiological measures (resting blood pressure and heart rate).

Objective 2: To objectively measure and compare physical activity levels, sedentary behaviour, and habitual sleep patterns of the OSA and CON groups using wrist-worn accelerometry.

Objective 3: To explore associations between CMD risk and physical activity parameters in the OSA and CON groups.

Aim 2: To systematically review the nature and efficacy of exercise interventions in reducing OSA severity and CMD risk factors in patients with OSA.

Objective 1: To assess the efficacy of an exercise programme on reducing OSA severity, improving fitness, body composition and sleep in patients with OSA.

Objective 2: To identify key components of these exercise interventions (e.g., mode of exercise, duration, frequency, intensity) associated with improved health outcomes in OSA patients.

CHAPTER 2: PHYSICAL ACTIVITY AND SEDENTARY BEHAVIOUR AMONG ADULTS BEING TREATED FOR OBSTRUCTIVE SLEEP APNOEA

2.1 INTRODUCTION

2.1.1 Rationale

Sedentary lifestyles have been associated with increased all-cause mortality. In addition, sedentary behaviour has been linked to a number of negative health outcomes including an increased body mass index (BMI) and waist circumference, cardiovascular disease, and certain metabolic disorders such as type II diabetes mellitus (T2DM), dyslipidaemia and metabolic syndrome (Park, Moon, Kim, Kong, & Oh, 2020). In contrast, regular physical activity has been associated with body weight maintenance, specifically in overweight individuals (Donnelly et al. 2009), reductions in blood pressure (Cornelissen & Fagard, 2005), and the prevention of cardiovascular disease (CVD) (Schuler, Adams, & Goto, 2013). Therefore, while promotion of regular physical activity is especially important for the general population to help prevent the development of chronic disease, it may be especially important in adults suffering from OSA.

There are some studies which report low levels of physical activity in individuals with OSA, attributable to the fatigue and lack of energy that characterize the clinical presentation of OSA, and potentially by the presence of obesity and other cardiometabolic diseases (CMD) (Hong & Dimsdale, 2003). As exercise has been associated with a reduction in OSA severity (Desplan et al. 2014), it may also be a useful means by which weight and the comorbidities associated with OSA could be managed. Individuals diagnosed with OSA and treated with CPAP therapy, for example, should experience an improved quality of life as their symptoms resolve, with fewer apnoeic and hyponoeic events, quality of sleep should improve, daytime sleepiness should be reduced, and daytime functioning should improve as well as their fatigue, but despite optimum CPAP treatment, these individuals often remain obese and suffer from cardiometabolic diseases (CMD). Thus, addressing weight loss through diet and physical activity is often advised as an adjunct therapy for individuals suffering from OSA.

Physical activity has been found to decrease with increased OSA severity (measured by the apnoea–hypopnea index (AHI)) (Chasens, Sereika, Houze, & Strollo, 2011; Jelke Verwimp, Lieveke Ameye, & Marie Bruyneel, 2013) including when controlling for age (Chasens et al. 2011) and BMI (Jelke Verwimp et al. 2013). The availability of physical activity monitoring has made the objective evaluation of physical activity in OSA patients in different settings possible. This includes describing the effects of CPAP on physical activity levels as well as specific physical activity quantification (Diamanti et al. 2013; Monique Mendelson et al. 2014; West, Kohler, Nicoll, & Stradling, 2009) during exercise rehabilitation programmes (Desplan et al. 2014; Monique Mendelson et al. 2014).

There is limited published data on the interplay between OSA and physical activity, BMI and cardiometabolic disease within the South African population. Only one study by Roche et al. (2021) was found, describing older adults randomly selected in a rural South African context, reported that 60,7% of the participants were overweight or obese, 61% were hypertensive, and 29% had undiagnosed OSA (Roche et al. 2021). The extent to which individuals who are being treated for OSA are physically active, however, is not known. Identifying any potential differences in physical activity habits observed in treated OSA individuals as compared to the general population may provide insights necessary for the successful implementation of physical activity promotion strategies designed to manage their comorbidities. Therefore, the purpose of this study is to describe the sleep and CMD risk profiles and habitual physical activity levels among individuals living with OSA in South Africa who are being treated using CPAP therapy.

2.1.2 Aim

Aim: To characterise and compare the sleep, physical activity and CMD risk profiles of adults living with OSA and being treated with CPAP therapy (OSA group) to age- and gender-matched adults without OSA (CON group).

Objective 1: To objectively measure and compare the habitual sleep patterns, physical activity intensity level and sedentary behaviour of the OSA and CON groups using wrist-worn accelerometry.

Objective 2: To characterise the CMD risk profile of both groups utilising medical history questionnaires (including diagnosed chronic conditions and medication use),

anthropometry (BMI, waist circumference (WC), neck circumference) and physiological measures (resting blood pressure and heart rate).

Objective 3: To explore associations between CMD risk factors and physical activity parameters in the OSA and CON groups.

2.2 MATERIALS AND METHODS

2.2.1 Participants

Thirty seven participants were recruited for this study and placed within one of two groups: the Obstructive Sleep Apnoea (OSA) group comprising of both male and female adults ($n=18$), previously diagnosed with moderate to severe OSA ($AHI \geq 15$) currently on CPAP therapy, and a control (CON) group also comprising male and female adults ($n=19$), but with no previous diagnosis of OSA nor symptoms or signs of OSA as confirmed on a validated OSA screening questionnaire STOP-Bang (Chung, Abdullah, & Liao, 2016), matched to the OSA group for age and gender. Participants were excluded if they were younger than 18y or older than 65y of age, not ambulatory (i.e., makes use of any walking aid), and reported any recent (two month) change in their usual physical activity or sleep habits. Exclusion criteria for the CON group also included (i) a previous diagnosis of OSA ($AHI \geq 5$) and (ii) a STOP-Bang score of >4 . Participants for both groups were recruited from the greater Cape Town and Johannesburg Metropolitan areas, by word of mouth and at sleep clinics. All participants were informed of the study purpose, risks and benefits and provided written informed consent indicating willingness to take part in the study (Appendix 1). This study was approved by the University of Cape Town's Faculty of Health Sciences Human Research Ethics Committee (Ref: 142/2021) and was performed under strict COVID-19 regulations.

2.2.2 Study design and overview

In this cross-sectional, observational study, all participants completed a detailed questionnaire (Appendix 2), and the investigator measured their weight, height, waist circumference (WC), and neck circumference, resting blood pressure, and heart rate. Participants were then given a small wrist-worn accelerometer to wear for the next seven days to measure their habitual sleep, physical activity and sedentary behaviour habits and were asked to simultaneously complete a sleep and physical activity diary (Appendix 3). They returned the sleep monitor and diary on their second visit to the clinic eight days later. All data collection took place at

either the Division of Physiological Sciences, University of Cape Town or in a medical practice in Johannesburg.

2.2.3. Detailed testing procedures

2.2.3.1 Questionnaire

The study questionnaire was administered to characterise participants and determine their eligibility for the study (Appendix 2). It captured individuals' demographic information, medical history, health status, lifestyle factors, current and past physical activity habits, daytime sleepiness and OSA risk. Smoking status was categorized as non-smoker, ex-smoker, occasional smoker, and current smoker. Alcohol status was categorized as consumer, non-consumer, or ex-consumer. Socio-economic status was determined using highest education level achieved (e.g., completed primary school, secondary school, or tertiary education), and employment status (employed/self-employed (part time or fulltime), unemployed, retired). Participants indicated whether they suffered from any diagnosed chronic diseases and indicated use of any chronic medication.

The 36-item Short Form Survey (SF-36) (Appendix 2) served as a measure of mental and physical health status and perceived quality of life. Participants are scored on 36 questions within eight domains of health: limitations in physical activities because of health problems, limitations in social activities because of physical or emotional problems, limitations in usual role activities because of physical health problems, bodily pain, general mental health (psychological distress and well-being), limitations in usual role activities because of emotional problems, vitality (energy and fatigue) and general health perceptions. Each score ranged from 0-100 with higher scores indicating a higher health related quality of life (HRQOL) (Ware & Sherbourne, 1992). This instrument addresses health concepts from the patient's perspective. There is no single overall score for the SF-36, rather individual scores for each of the eight domains. Current and past physical activity questions were included in Appendix 2 of this analysis.

The Epworth Sleepiness Scale (ESS) (Appendix 2) was used to quantify daytime sleepiness. Participants were asked to assess their likelihood of dozing off or falling asleep in eight scenarios, with 0 indicating "would never doze" and 3 indicating "high chance of dozing". Item scores were summed to generate a total ESS score between 0-24. Higher scores indicated

higher levels of daytime sleepiness (Johns, 1991). Scores of “normal” daytime sleepiness range from 0- 10, with scores of 11-24 representing excessive daytime sleepiness.

The STOP-Bang questionnaire (Appendix 2) for OSA was primarily used to ensure eligibility of the CON group participants. It comprised of eight yes/no questions around snoring, daytime tiredness, observed apnoeic events, high blood pressure (resting systolic blood pressure (SBP) ≥ 140 mmHg and/or a resting diastolic blood pressure (DBP) ≥ 90 mmHg), BMI > 35 kg/m², age > 50 y, neck circumference > 43 cm (males) or > 41 cm (females) and gender (male) (Chung et al. 2016). Scores of 0-2: low risk for OSA, 3-4: moderate risk, 5-8: high risk.

2.2.3.2 Habitual sleep and physical activity measures

Participants were asked to wear an accelerometer (Actiwatch Spectrum Pro, Philips Respironics, Koninklijke Philips N.V, Amsterdam, Netherlands) on their non-dominant wrist 24h per day for seven consecutive days and kept a simple sleep and physical activity diary. They were allowed to remove the device while bathing / showering and used an event marker button to indicate the beginning and end of daytime naps and night-time sleep periods. The purpose of the actigraphy was to measure habitual sleep-wake patterns as well as sedentary and physical activity behaviours. A dataset was considered to be valid if there were a least five nights of valid sleep data, one of which needed to be a weekend night (Friday or Saturday). The average number of sleep nights obtained for our participants was 219, of which 153 represented weeknights and 66 were weekend nights. Timing of sleep periods was established manually based on published guidelines (Chow et al. 2016), making use of the event marker and sleep diary to confirm sleep and nap periods. The data were processed using Philips Actiware software (v.6.0.9, Philips Actiware, Philips Respironics, Koninklijke Philips N.V, Amsterdam, Netherlands). Outcome variables included nocturnal bedtime, wake-up time, time-in-bed, total sleep time, sleep onset latency, sleep efficiency, arousal index, and midpoint of sleep. Midpoint of sleep was calculated by subtracting half of the time-in-bed duration from wake-up time. Daytime naps were identified, and their time-in-bed and total sleep time reported. Regularity of nocturnal sleep timing (bedtime and wake-up time) and duration (time-in-bed and total sleep time) were determined by calculating each person's seven-day standard deviation for each variable. We used 24h total sleep time to determine the number of participants meeting the recommended sleep duration guidelines (7-9h) (Hirshkowitz et al. 2015). Participants reported on how satisfied (not at all, a little, somewhat, quite, or very) they were with each night's sleep and how refreshed (not at all, slightly, somewhat, well, or very well) they felt on waking, in the sleep diary. Sedentary and physical

activity behaviours were also derived from the Actiwatch, which collected movement data measured in counts per minute (cpm) continuously in 15s epochs. Activity counts for each 60s epoch was determined by averaging the four adjacent but non-overlapping 15s epochs, and then, based on previously determined cut-points (Kemp et al. 2020) (described in detail below in section 2.2.4), we estimated daily total cumulative physical activity during waking hours, as well as absolute (h/day) and relative (%) time spent in sedentary, low, moderate, and vigorous intensity physical activity each day. These daily values for each participant were then used to calculate their mean values for all seven days of measurement. We also used the physical activity data to determine how many participants met guidelines (American College of Sports et al. 2018). Based on these ACSM guidelines for physical activity, to achieve health benefits, most adults should accumulate 30–60 min/d (≥ 150 min/wk).

2.2.3.3 Cardiometabolic disease risk profile

Height (m), weight (kg), WC (cm) and neck circumference (cm) of all participants were measured by the same investigator. BMI was calculated as weight (kg) / height (m)². Participants were classified as normal weight if BMI was <25 kg/m², overweight if BMI ≥ 25 kg/m² but <30 kg/m² and obese if BMI ≥ 30 kg/m² (American College of Sports et al. 2018). Resting blood pressure and resting heart rate were determined with participants remaining in a seated position for 10min before the measurement was taken. Readings were taken at the time of day that the participant attended the first visit (ranged from 09h00 – 18h00), twice at 1min intervals using an appropriately sized cuff with a manual blood pressure monitor (Palm Satin Elite Blood Pressure Meter Aneroid Sphygmomanometer and Stethoscope, Hi-Care INT, Muizenberg, South Africa). Resting heart rate was taken by the facilitator placing the second and third fingers between the bone and the tendon over the radial artery — which is located on the thumb side of the wrist, of the participant, once a pulse was felt, a timer for 60 seconds was started and the count of the number of beats was recorded for that minute (American College of Sports et al. 2018). Resting mean Arterial Pressure (MAP) was calculated to determine the average blood pressure in a person's blood vessels during a single cardiac cycle, as $MAP = DBP + 1/3(SBP - DBP)$ or $MAP = DBP + 1/3(HR)$ (DeMers & Wachs, 2022).

2.2.4 Data and statistical analyses

Actigraphy datasets to measure free-living sleep and physical activity were considered valid if a person had at least four working days and at least one non-working day, and the device was worn for a minimum of 20h in each 24h period. Periods of non-wear time were marked as

'excluded' intervals and were omitted from the final analysis. Actigraphy data were collected over an average monitoring period of 6.7 days. Physical activity count data were converted into 60s epochs and were subsequently analysed epoch-by-epoch. A count is reflected by the peak acceleration detected over each epoch. Waking movement data were filtered by 'active' intervals, whilst 24h physical activity pattern data were filtered by both 'active' and 'rest' intervals. To account for inter-individual differences in total waking time, count data were normalized using the total waking time recorded per participant and presented as relative values (% time spent in each physical activity intensity category), in addition to their absolute values (minutes per day spent in each physical activity intensity category). Sedentary behaviour was characterized using a count cut-point of <256cpm; whilst moderate and vigorous physical activity intensities were characterized using count cut-points of >418cpm and >720cpm, respectively (Kemp et al. 2020). Light intensity physical activity was defined as counts between the thresholds for sedentary behaviour and moderate physical activity intensity ($257\text{cpm} \leq \leq 417\text{cpm}$) (Kemp et al. 2020). The dose of physical activity at each count threshold for each participant was averaged over each day of monitoring.

Data are presented as mean $\pm$ standard deviation, median (interquartile range), or count (%). The Shapiro-Wilk test was used to determine whether the data were normally distributed. Between groups comparisons were conducted using independent t-tests, Mann-Whitney U tests, Fisher's Exact or Chi Squared tests. Linear and logistic regression analyses were conducted to explore associations between CMD risk (dependent) and physical activity (independent) variables. Since the models included all participants, we first tested for possible interactions between group (OSA and CON) with the independent variables. For models in which there were no group-by-physical activity variable interactions, the interaction term was removed from the model and main effects for group and physical activity were reported. Alternatively, the interaction term was retained in the model. All statistical analyses were performed using Stata version 10 software (StataCorp LP, Texas, USA). Statistical significance was accepted when $p < 0.05$.

2.3 RESULTS

2.3.1 Participant characteristics

The descriptive characteristics of the OSA and CON group participants are presented in Table 2.1. There were no significant differences between the groups with respect to any of the descriptive variables. The general health and medical condition characteristics of both groups

are presented in Table 2.2. Although all 18 OSA participants were being treated with a CPAP device, on diagnosis of OSA their mean AHI was 50.0 ± 28.0 events/h, with 31.25% being classified as having moderate and 68.75% as having severe OSA. The OSA group had a significantly higher BMI and more of the OSA group were classified as obese compared to the CON group (both $p < 0.001$). In addition, the OSA group had larger neck circumference ($p < 0.001$), WC ($p < 0.001$) and higher resting SBP ($p = 0.039$) than the CON group. More individuals in the OSA group suffered from diagnosed chronic conditions (89%) than the CON group (47%, $p = 0.007$). Furthermore, the OSA group reported more diagnosed CMD (72%) than the CON group (32%, $p = 0.013$), and specifically, more people in the OSA group report diagnosed hypertension ($p = 0.033$), diabetes ($p = 0.019$), gout ($p = 0.032$), thyroid ($p = 0.032$) and mood disorders ($p = 0.020$) than those individuals in the CON group. There were no significant differences observed between the groups for any of the SF-36 survey categories as illustrated in Table 2.3.

Table 2.1: Descriptive characteristics of participants.

	OSA (n=18)	CON (n=19)	p-value
Age (y)	59 [49-62]	56 [50-63]	0.879
Sex (male)	14 (78)	15 (79)	0.931
Smoke status:			0.435
Non-smoker	12 (67)	15 (79)	
Ex- smoker	4 (22)	2 (11)	
Occasional smoker	0	1 (5)	
Smoker	2 (11)	1 (5)	
Alcohol status:			0.911
Consumer	12 (67)	13 (68)	
Non consumer	6 (33)	6 (32)	
Ex-consumer	0 (0)	0 (0)	
Highest education level completed:			0.089
Primary school	1 (5)	0 (0)	
Secondary school	5 (28)	2 (11)	
Tertiary education	12 (67)	17 (89)	
Employment status:			0.460
Employed full-time	12 (67)	14 (74)	
Employed part-time	3 (16.5)	5 (26)	
Unemployed	0	0	
Retired	3 (16.5)	0	
Working hours per week	30.4 $\pm$ 19.3	37.42 $\pm$ 17.39	0.412

Data are presented as mean $\pm$ standard deviation, median [interquartile range] or count (%). OSA: Obstructive sleep apnoea group, CON: Control group. P-values represent between group comparisons made using independent t-tests, Mann-Whitney U, Chi-squared or Fisher's Exact tests.

Table 2.2: General health and medical conditions of participants.

	OSA (n=18)	CON (n=19)	p-value
AHI * (events/h)	50.0 $\pm$ 28.0	-	-
BMI (kg/m ²)	38.9 $\pm$ 8.6	27.4 $\pm$ 4.7	<0.001
Overweight	3 (17)	8 (42)	0.091
Obese	15 (83)	5 (26)	<0.001
NC (cm)	45.3 $\pm$ 5.1	38 $\pm$ 2.4	<0.001
WC (cm)	120.5 $\pm$ 16.7	97.2 $\pm$ 13.3	<0.001
Resting SBP (mmHg)	130.0 $\pm$ 9.0	124.0 $\pm$ 8.0	0.039
Resting DBP (mmHg)	81.0 $\pm$ 7.0	79.0 $\pm$ 7.0	0.456
Resting MAP (mmHg)	97.0 $\pm$ 5.0	94.0 $\pm$ 7.0	0.107
Resting HR (bpm)	69.0 $\pm$ 10.0	67.0 $\pm$ 10.0	0.626
Total number with chronic conditions	16 (89)	9 (47)	0.007
CMD:	13 (72)	6 (32)	0.013
Hypertension	10 (55)	4 (21)	0.033
Hypercholesterolemia	4 (22)	3 (15)	0.622
Diabetes	7 (38)	1 (5)	0.019
Mood disorders*	8 (44)	2 (10)	0.020
Asthma	2 (11)	1 (5)	0.521
Gastrointestinal complaints (self-reported)	3 (16)	2 (10)	0.590
Thyroid condition	4 (22)	0 (0)	0.032
Allergic rhinitis / sinusitis	1 (6)	3 (15)	0.323
Gout	4 (22)	0 (0)	0.032
Medications for:			
Hypertension	10 (55)	4 (21)	0.033
Hypercholesterolemia	4 (22)	3 (15)	0.622
Diabetes	7 (38)	1 (5)	0.014
Gout	4 (22)	0 (0)	0.032
Sleep	2 (11)	1 (5)	0.521
Mood	8 (44)	2 (20)	0.022

Data are presented as mean $\pm$ standard deviation or count (%). OSA: Obstructive sleep apnoea group, CON: Control group, AHI: apnoea hypopnea index, BMI: body mass index,

neck circumference: neck circumference, WC: waist circumference, SBP: systolic blood pressure, DBP: diastolic blood pressure, MAP: mean arterial pressure, HR: heart rate, CMD: cardiometabolic disease. *AHI value on diagnosis of condition. P-values represent between group comparisons made using independent t-tests, Chi-squared or Fisher's Exact tests.

Table 2.3: Participants' self-reported health scores based on the SF-36 Survey.

	OSA (n=18)	CON (n=19)	p-value
Physical functioning	85 [60-95]	95 [90-100]	0.865
Role limitations due to physical health	100 [25-100]	75 [50-100]	0.621
Role limitations due to emotional health	100 [0-100]	100 [33-100]	0.688
Energy/Fatigue	50 [40-50]	50 [45-60]	0.543
Emotional wellbeing	32 [32-40]	38 [32-40]	0.176
Social functioning	100 [75-100]	87.5 [75-100]	0.743
Pain	80 [68-80]	80 [80-100]	0.483
General health	70 [55-75]	75 [60-85]	0.151

Data are presented as median [interquartile range]. OSA: Obstructive sleep apnoea group, CON: Control group. P-values represent between group comparisons made using Mann-Whitney U tests.

2.3.2 Sleep and physical activity characteristics of the obstructive sleep apnoea and control groups

The self-report and measured sleep parameters of the two groups are presented in Table 2.4. By design, the OSA group had a higher STOP-Bang score (5.11 ± 1.32) than the CON group (2.16 ± 1.42 , $p < 0.001$). One individual in the CON group was classified as high risk for OSA. On follow-up, this participant was found to be suffering from sinus-related allergies and we therefore retained him in the CON group. The OSA group had higher ESS scores ($p = 0.030$), more individuals with excessive daytime sleepiness ($p = 0.007$) and also woke up later than the CON group ($p = 0.035$), but no other sleep variables differed between the groups. 33% of the OSA group and 16% of the CON group met the 7-9h sleep duration guidelines.

Based on their sleep diary, 11 (61%) of the OSA group reported being currently physically active, while 15 (79%) of the CON group reported being active ($p = 0.242$). The OSA group reported exercising on 3.11 ± 2.52 d/wk and the CON group on 3.53 ± 2.34 d/wk during the

week of monitoring ($p=0.608$). The actigraphy-derived sedentary behaviour and physical activity data of all participants is displayed in Table 2.5. The OSA group had lower total daily counts for moderate ($p=0.014$) and vigorous ($p=0.023$) intensity physical activity and spent fewer hours per day engaging in moderate ($p=0.010$) and vigorous ($p=0.030$) intensity physical activity compared to the CON group. The OSA group also spent relatively more time each day in sedentary behaviour ($p=0.029$) and less time in moderate ($p=0.017$) and vigorous ($p=0.042$) intensity physical activity than the CON group.

Based on the ACSM guidelines for physical activity, to achieve health benefits, most adults should accumulate 30–60 min/d (≥ 150 min/wk) of moderate intensity exercise. None (0%) of the OSA group and 11% of the CON group met the ACSM guidelines for moderate physical activity (American College of Sports et al. 2018).

Table 2.4: Sleep characteristics of the participants.

	OSA (n=18)	CON (n=19)	p-value
ESS score	10 [5-11]	6 [5-8]	0.030
Excessive daytime sleepiness	6 (33)	0 (0)	0.007
Actigraphy Data			
Nocturnal sleep:			
Bedtime (hh:mm)	23:00 ± 0:50	22:49 ± 0:41	0.564
Wake-up time (hh:mm)	06:50 ± 0:43	06:23 ± 0:40	0.035
Time-in-bed (h)	7.80 ± 0.75	7.60 ± 0.75	0.378
Total sleep time (h)	6.89 ± 0.65	6.50 ± 0.56	0.137
Sleep onset latency (min)	6.0 [4.3-12.1]	7.2 [4.1-19.1]	0.485
Sleep efficiency (%)	88.8 ± 3.6	87.1 ± 5.1	0.378
Midsleep (hh:mm)	02:55 ± 0:41	02:36 ± 0:34	0.153
Arousal index (arousals/h)	6.7 ± 2.5	7.0 ± 2.8	0.785
Bedtime regularity (h)	0.72 [0.45-1.13]	0.82 [0.65-1.07]	0.516
Wake-up time regularity (h)	0.73 [0.66-1.15]	0.77 [0.57-0.88]	0.601
Time-in-bed regularity (h)	1.05 [0.75-1.30]	0.98 [0.70-1.05]	0.887
Total sleep time regularity (h)	0.59 ± 0.24	1.05 ± 0.36	0.739
24h sleep:			
Time-in-bed (h)	7.57 ± 0.47	7.46 ± 0.45	0.504
Total sleep time (h)	6.59 ± 0.40	6.38 ± 0.33	0.107
Naps:			
Number of people napping	9 (50)	14 (74)	0.143
Nap time-in-bed (h)	0.57 ± 0.35	0.57 ± 0.31	0.770
Nap total sleep time (h)	0.38 ± 0.33	0.39 ± 0.33	0.953
Sleep satisfaction score	72.6 ± 22.7	70.9 ± 12.7	0.784
Sleep refresh score	70.5 ± 19.0	64.9 ± 13.2	0.315

Data are presented as mean ± standard deviation, median [interquartile range] or count (%). OSA: Obstructive sleep apnoea group, CON: Control group, ESS: Epworth Sleepiness Scale. P-values represent between group comparisons made using independent t-tests, Mann-Whitney U, Chi-squared or Fisher's Exact tests.

Table 2.5: Accelerometry-derived physical activity characteristics of participants.

	OSA (n=18)	CON (n=19)	p-value
Total sedentary behaviour (counts/day)	3910 ± 1052	3501 ± 789	0.187
Total light PA (counts/day)	734 ± 173	888 ± 330	0.087
Total moderate PA (counts/day)	697 [384 - 807]	832 [696 - 1122]	0.014
Total vigorous PA (counts/day)	192 [84 - 359]	362 [228 - 487]	0.023
Sedentary behaviour time (h/day)	10.94 ± 2.11	9.88 ± 1.86	0.116
Light PA time (h/day)	2.11 ± 0.56	2.50 ± 0.87	0.115
Moderate PA time (h/day)	1.80 ± 0.77	2.49 ± 0.77	0.010
Vigorous PA time (h/day)	0.57 [0.26 - 0.95]	1.01 [0.67 - 1.51]	0.030
Relative sedentary time (%)	70.12 ± 11.14	61.94 ± 10.65	0.029
Relative light PA time (%)	13.60 ± 3.69	15.68 ± 5.35	0.179
Relative moderate PA time (%)	11.59 ± 4.95	15.68 ± 5.02	0.017
Relative vigorous PA time (%)	3.81 [1.64 - 6.08]	6.05 [4.27 - 9.47]	0.042
Total waking time (h/day)	15.59 ± 1.17	15.93 ± 0.75	0.287

Data are presented as mean ± standard deviation or median [interquartile range]. OSA: Obstructive sleep apnoea group, CON: Control group, physical activity: physical activity. P-values represent between group comparisons made using independent t-tests or Mann-Whitney U tests.

2.3.3 Associations between cardiometabolic disease risk and physical activity variables

In each of the analyses, we first tested for interaction effects between group (OSA and CON) and the independent variables (sedentary behaviour and physical activity). These results are presented in Appendix 5 (Tables A2.1 – A2.5). There were no group-by-physical activity interaction effects in any of the models, with the exception of the model in which diary-derived weekly physical activity time was regressed against hypertension (Table A2.4, $p=0.045$). For models with non-significant interaction effects, the interaction term was removed and models with only simple main effects are presented on pooled data from both groups. BMI was associated with both objectively-measured relative VPA (% , $p=0.002$) and absolute VPA (min/day, $p=0.005$), such that even when accounting for group in the models, participants with lower levels of daily VPA had higher BMIs (Table 2.6). There were also group effects for BMI in each model, indicating that even when accounting for SB and physical activity, participants in the OSA group had higher BMIs than those in the CON group (all $p<0.001$). Together, SB or physical activity and group explained between 43% (diary-derived weekly physical activity time) and 55% (absolute VPA) of variance in BMI in the models.

Similarly, WC was associated with both objectively-measured relative VPA (% , $p=0.020$) and absolute VPA (min/day, $p=0.011$), such that even when taking group into account, participants with lower levels of daily VPA had higher WC values (Table 2.7). There were also group effects for each WC model such that even when accounting for SB and physical activity, participants in the OSA group had higher WCs than those in the CON group (all $p<0.001$). Overall, the SB or physical activity and group variables explained between 39% (diary-derived weekly physical activity time) and 50% (absolute VPA) of variance in WC in these models., indicating that for every additional diary-derived minute of physical activity per week, the OSA group had higher odds to have hypertension compared to the CON group.

Having a diagnosed chronic condition was not associated with any of the SB or physical activity variables (Table 2.8). There were also only group effects for objectively-measured sedentary behaviour time (min/d, $p=0.047$) and diary-derived weekly physical activity time (min/week, $p=0.025$), although the latter overall model was not significant. Thus, only when accounting for SB time were the OSA group observed to have more chronic conditions than

the CON group (Table 2.8). These models, were however, generally weak explaining only between 15 and 22% of variance in number of individuals reporting diagnosed chronic conditions.

Having diagnosed hypertension was not associated with any of the SB or physical activity variables even when accounting for group, with the exception of diary-derived weekly physical activity time (Table 2.9). In this latter model, there was a weak group-by-physical activity variable interaction ($p=0.045$) indicating that the relationship between hypertension and diary-derived weekly physical activity time differs between the two groups. Post hoc analyses suggest that amongst the OSA participants, those reporting more physical activity in their weekly diary, are more likely to belong to the hypertension group, while among the CON group, those who report more physical activity in their weekly diary are more likely to be non-hypertensive.

Having diagnosed diabetes was not associated with any of the SB or physical activity variables, even when accounting for group (Table 2.10). There were, however, group effects for daily SB time (min/d: $p=0.030$ and percentage: $p=0.032$), daily MPA time (min/d: $p=0.030$ and percentage: $p=0.030$) and diary-derived weekly physical activity time ($p=0.036$) models such that when accounting for the SB and physical activity variables, individuals belonging to the OSA group were more likely to report suffering from a diagnosed chronic condition than those in the CON group.

Table 2.6. Linear regression analyses looking at associations between BMI (dependent variable) with sedentary behaviour, physical activity, and group (independent variables) among all participants (n=37).

	Model 1 SB (%)	Model 2 MPA (%)	Model 3 VPA (%)	Model 4 SB (min/d)	Model 5 MPA (min/d)	Model 6 VPA (min/d)	Model 7 Diary-derived weekly PA duration min/wk
PA effect	0.12 (-0.09, 0.34), p=0.260	-0.35 (-0.81, 0.12), p=0.140	-0.81 (-1.40, -0.23), p=0.002	0.01 (-0.01, 0.03), p=0.327	-0.04 (-0.09, 0.01), p=0.102	-0.09 (-0.15, -0.03), p=0.005	-0.01 (-0.07, 0.04), p=0.638
Group effect	10.50 (5.62, 15.39), p<0.001	10.08 (5.20, 14.96), p<0.001	9.85 (5.50, 14.20), p<0.001	10.88 (6.12, 15.63), p<0.001	9.79 (4.87, 14.71), p<0.001	9.67 (5.37, 13.98), p<0.001	11.29 (6.58, 16.00), p<0.001
Overall model	<i>F: 13.78, R²: 0.45,</i> p<0.001	<i>F: 14.63, R²: 0.46,</i> p<0.001	<i>F: 19.54, R²: 0.53,</i> p<0.001	<i>F: 13.50, R²: 0.44,</i> p<0.001	<i>F: 15.09, R²: 0.47,</i> p<0.001	<i>F: 20.60, R²: 0.55,</i> p<0.001	<i>F: 12.83, R²: 0.43,</i> p<0.001

Data for the main and group effects are presented as beta coefficients with 95% confidence intervals. BMI: body mass index, SB: sedentary behaviour, MPA: moderate intensity physical activity, VPA: vigorous intensity physical activity, PA: physical activity.

Table 2.7. Linear regression analyses looking at associations between WC (dependent variable) with sedentary behaviour, physical activity, and group (independent variables) among all participants (n=37).

	Model 1 SB (%)	Model 2 MPA (%)	Model 3 VPA (%)	Model 4 SB (min/d)	Model 5 MPA (min/d)	Model 6 VPA (min/d)	Model 7 Diary-derived weekly PA duration min/wk
PA effect	0.40 (-0.06, 0.86), p=0.084	-0.82 (-1.83, 0.19), p=0.108	-1.58 (-2.90, -0.26), p=0.020	0.03 (-0.01, 0.07), p=0.145	-0.10 (-0.21, 0.01), p=0.071	-0.18 (-0.32, -0.05), p=0.011	-0.00 (-0.12, 0.13), p=0.942
Group effect	20.00 (9.54, 30.46), p<0.001	19.63 (9.27, 30.58), p<0.001	20.09 (10.30, 29.87), p<0.001	21.29 (11.04, 31.54), p<0.001	19.16 (8.46, 29.87), p<0.001	19.65 (9.99, 29.31), p<0.001	23.36 (12.98, 33.74), p<0.001
Overall model	<i>F: 13.35, R²: 0.44,</i> p<0.001	<i>F: 12.99, R²: 0.43,</i> p<0.001	<i>F: 15.62, R²: 0.48,</i> p<0.001	<i>F: 12.59, R²: 0.43,</i> p<0.001	<i>F: 13.61, R²: 0.44,</i> p<0.001	<i>F: 16.68, R²: 0.50,</i> p<0.001	<i>F: 10.77, R²: 0.39,</i> p=0.002

Data for the main and group effects are presented as beta coefficients with 95% confidence intervals. WC: waist circumference, SB: sedentary behaviour, MPA: moderate intensity physical activity, VPA: vigorous intensity physical activity, PA: physical activity.

Table 2.8. Logistic regression analyses looking at associations between individuals with diagnosed chronic conditions (dependent variable) with sedentary behaviour, physical activity, and group (independent variables) among all participants (n=37).

	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6	Model 7
	SB (%)	MPA (%)	VPA (%)	SB (min/d)	MPA (min/d)	VPA (min/d)	Diary-derived weekly PA duration min/wk
PA effect	0.03 (-0.02, 0.08), p=0.274	-0.08 (-0.20, 0.04), p=0.171	-0.14 (-0.29, -0.02), p=0.085	0.00 (-0.00, 0.01), p=0.289	-0.01 (-0.02, 0.00), p=0.157	-0.01 (-0.03, 0.00), p=0.083	-0.00 (-0.02, 0.01), p=0.919
Group effect	1.14 (-0.09, 2.38), p=0.069	1.05 (-0.19, 2.29), p=0.093	1.11 (-0.06, 2.28), p=0.062	1.22 (0.02, 2.42), p=0.047	1.01 (-0.25, 2.27), p=0.111	1.09 (-0.08, 2.26), p=0.066	1.37 (0.18, 2.57), p=0.025
Overall model	<i>F: 3.60, R²: 0.17,</i> p=0.038	<i>F: 4.02, R²: 0.19,</i> p=0.027	<i>F: 4.72, R²: 0.22,</i> p=0.016	<i>F: 3.55, R²: 0.17,</i> p=0.040	<i>F: 4.10, R²: 0.19,</i> p=0.025	<i>F: 4.74, R²: 0.22,</i> p=0.015	<i>F: 2.88, R²: 0.15,</i> p=0.070

Data for the main and group effects are presented as odds ratio with 95% confidence intervals. SB: sedentary behaviour, MPA: moderate intensity physical activity, VPA: vigorous intensity physical activity, PA: physical activity.

Table 2.9. Logistic regression analyses looking at associations between individuals diagnosed with hypertension (dependent variable) with sedentary behaviour, physical activity, and group (independent variables) among all participants (n=37).

	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6	Model 7
	SB (%)	MPA (%)	VPA (%)	SB (min/d)	MPA (min/d)	VPA (min/d)	Diary-derived weekly PA duration min/wk
PA effect	1.01 (0.94, 1.08), p=0.774	0.97 (0.84, 1.13), p=0.766	0.96 (0.79, 1.17), p=0.677	1.00 (0.99, 1.01), p=0.850	1.00 (0.98, 1.01), p=0.735	1.00 (0.98, 1.02), p=0.700	0.96 (0.89, 1.03), p=0.236
Group effect	3.34 (0.94, 20.01), p=0.060	4.29 (0.91, 20.16), p=0.065	4.33 (0.98, 19.14), p=0.053	4.87 (1.08, 21.88), p=0.039	4.20 (0.88, 20.11), p=0.073	4.34 (0.98, 19.28), p=0.053	0.38 (0.03, 4.23), p=0.432

PA-by-group interaction effect	-	-	-	-	-	-	1.10 (1.00, 1.20), p=0.045
Overall model	<i>LR chi²: 4.88</i> p=0.087	<i>LR chi²: 4.88</i> p=0.087	<i>LR chi²: 4.97</i> p=0.083	<i>LR chi²: 4.83</i> p=0.089	<i>LR chi²: 4.91</i> p=0.086	<i>LR chi²: 4.94</i> p=0.085	<i>LR chi²: 12.66,</i> p=0.005

Data for the main, group and interaction effects are presented as odds ratios with 95% confidence intervals. SB: sedentary behaviour, MPA: moderate intensity physical activity, VPA: vigorous intensity physical activity, PA: physical activity.

Table 2.10. Logistic regression analyses looking at associations between individuals diagnosed with diabetes (dependent variable) with sedentary behaviour, physical activity, and group (independent variables) among all participants (n=37).

	Model 1 SB (%)	Model 2 MPA (%)	Model 3 VPA (%)	Model 4 SB (min/d)	Model 5 MPA (min/d)	Model 6 VPA (min/d)	Model 7 Diary-derived weekly PA duration min/wk
PA effect	0.99 (0.91, 1.07), p=0.719	1.05 (0.88, 1.25), p=0.597	0.91 (0.71, 1.17), p=0.464	1.00 (0.99, 1.01), p=0.723	1.01 (0.99, 1.02), p=0.579	1.00 (0.96, 1.02), p=0.443	1.00 (0.97, 1.03), p=0.843
Group effect	13.01 (1.25, 135.92), p=0.032	14.21 (1.29, 156.04), p=0.030	9.68 (1.00, 93.85), p=0.050	12.52 (1.27, 123.50), p=0.030	14.65 (1.30, 165.40), p=0.030	9.50 (0.97, 92.67), p=0.053	11.05 (1.17, 104.14), p=0.036
Overall model	<i>LR chi²: 6.87</i> p=0.032	<i>LR chi²: 7.02</i> p=0.030	<i>LR chi²: 7.32</i> p=0.026	<i>LR chi²: 6.87</i> p=0.032	<i>LR chi²: 7.05</i> p=0.029	<i>LR chi²: 7.39</i> p=0.025	<i>LR chi²: 6.78</i> p=0.034

Data for the main and group effects are presented as odds ratios with 95% confidence intervals. SB: sedentary behaviour, MPA: moderate intensity physical activity, VPA: vigorous intensity physical activity, PA: physical activity.

2.4 DISCUSSION

The most important findings of this study are marked differences displayed in the OSA group's objectively-measured moderate and vigorous intensity physical activity parameters compared to those of the CON group. The OSA cohort in this study spent relatively more time being sedentary (i.e., low-energy activities), and relatively less time performing activities that expend more energy (i.e., both absolute and relative moderate, and vigorous intensity exercise) compared to the CON group. One might hypothesise that this explains why, despite their management of OSA with CPAP, the OSA group had more adiposity and suffered from more chronic diseases, including hypertension and T2DM than the CON participants (Hall, Singh, Mukherjee, & Palmer, 2020). We also observed strong associations between objectively-measured vigorous intensity exercise with BMI and waist circumference, thus suggesting that being sufficiently active at higher intensities is of importance in addressing adiposity in these individuals. The lack of any interaction effect, however, suggests that OSA participants who become more vigorously physically active should have the same response in reducing BMI and waist circumference as the CON group. Furthermore, the group effect suggests that regardless of sedentary behaviour or physical activity, both BMI and waist circumference were still higher in the OSA group, thus factors other than lower levels of physical activity likely contribute to markers of adiposity among OSA participants. These findings are noted against a backdrop of no differences in sleep characteristics between the groups, with the exception that later wake times were observed in OSA participants.

Mechanisms other than being less active, and not measured in this study, may explain the higher incidence of chronic diseases, and specifically hypertension and diabetes among the OSA group in this study. This is supported by the observation of strong group effects in all the models examined in this study, suggesting that regardless of the differences in objectively-measured physical activity intensity levels, including the increased time spent participating in low-energy expenditure activities such as sedentary behaviour, the OSA participants were more likely to suffer from chronic conditions, including hypertension and diabetes. These findings are valuable as determining physical activity and sedentary behaviour among those with moderate to severe OSA can assist in understanding the current behaviours of OSA individuals being treated with CPAP therapy and provide impactful guidance on lifestyle changes that may improve comorbidities. These findings may also provide insights into pathogenic mechanisms of some of the additional findings within this OSA cohort discussed

below, which include a higher BMI, waist circumference and neck circumference as well as more chronic conditions such as diabetes and hypertension, all of which might add to OSA severity and risk.

Similar to our findings, Simpson et al.'s (2015) cohort of men and women (mean age 51 years) with OSA reported less moderate to vigorous intensity physical activity compared to their CON group, measured using the Active Australian Survey, with no mention of other therapies (i.e., CPAP). Within their OSA group, only 48% of the men and 42% of the women participants self-reported ≥ 150 min/wk of moderate-to-vigorous intensity exercise, whereas 69% of the men and 66% of the women without OSA reported achieving that threshold of exercise (Simpson et al. 2015). In addition, more than one cross-sectional study reviewing self-reported physical activity consistently reported a lower severity of OSA in individuals with higher physical activity levels (Hall et al. 2020; Murillo et al. 2016). Due to the cross-sectional study designs, however, it cannot be determined whether the observed associations are attributed to the compromised ability to participate in exercise as a consequence of certain hallmark OSA symptoms (e.g., sleepiness, fatigue, daytime dysfunction), or whether being more active directly improves OSA symptoms. Furthermore, there was no mention of adjunctive therapies (i.e., CPAP).

From our cohort's self-reported physical activity data, we observed that the relationship between hypertension and diary-derived weekly physical activity time differed between our OSA and CON groups. The OSA participants who reported more weekly physical activity time were more likely to have hypertension, while in contrast the CON participants who reported more weekly physical activity time were more likely to be non-hypertensive. One might conclude that those OSA participants diagnosed with hypertension are trying to be more physically active in order to better manage their condition and improve their health. Among the CON participants, however, the usual relationship between physical activity and hypertension is observed, which is that individuals who are more physically active are less likely to have hypertension, lowering their risk of heart disease (Hegde & Solomon, 2015).

Two prospective studies provide further insights into the role that physical activity may play in the development of OSA (Awad, Malhotra, Barnet, Quan, & Peppard, 2012; Liu et al. 2022). In a longitudinal study, Awad et al. (2012) reported an increase in exercise to be associated with a reduced incidence of sleep disordered breathing, thought to be mediated by changes in body physique and that decreasing exercise was associated with worsening of apnoea

hypopnea index (Awad et al. 2012). Further, Liu et al. (2022) indicated that several metabolic factors, including body mass index and waist circumference, were associated with sedentary behaviour and OSA incidence, while higher levels of physical activity and fewer sedentary hours were associated with lower OSA incidence (Liu et al. 2022).

We observed that when accounting for objectively measured sedentary behaviour, moderate intensity physical activity, and self-reported physical activity time, the OSA group was more likely to have T2DM. Current evidence indeed points towards an association between OSA and diabetes (insulin resistance and glucose intolerance). A significant number of patients with T2DM suffer from undiagnosed OSA (Reutrakul & Mokhlesi, 2017). Sleep debt and/or disrupted sleep may lead to increased appetite and less physical activity which may lead to obesity with a subsequent increased risk of decreased insulin sensitivity and beta-cell dysfunction. The increased BMI often associated with T2DM may in turn increase the risk of OSA. Recent studies however support a bidirectional association between OSA and T2DM, independent of obesity (T. Y. Huang et al. 2018). This raises interesting questions regarding the possible mechanistic pathways involved. In our study, however, there are no obvious differences in sleep parameters between the CPAP-treated OSA participants and the control group, which suggests that their current sleep is not associated with diabetes. Perhaps a prior history of sleep debt or disrupted sleep set in motion the development of T2DM in the OSA participants, of which subsequent management of their condition has not been able to reverse. Or perhaps some factor other than poor sleep predisposed this group to diabetes.

Chronic systemic inflammation, commonly seen in obesity and diabetes, is associated with a higher OSA prevalence. The intermittent hypoxia and sleep fragmentation that occur as a result of OSA may similarly increase oxidative stress, sympathetic activity, anterior hypothalamic axis (HPA) activation, systemic inflammation and circulating adipokines resulting in metabolic changes that predispose to the development of T2DM. The possible role of diabetic neuropathy, i.e. impaired central control of respiration and upper airway neural reflexes, may further exacerbate OSA severity (Reutrakul & Mokhlesi, 2017). Considering the possible interplay between these proposed pathways, these studies suggest that interventions targeting obesity and metabolic pathways are beneficial for the treatment of OSA (T. Huang et al. 2018). Notably, successful weight management can improve OSA and glucose control. There are few studies as to whether CPAP therapy treatment of OSA improves glucose metabolism, but conflicting findings were reported with CPAP therapy treatment in a pre-diabetic group of OSA patients improving insulin sensitivity and overall glucose control, with

limited benefit in individuals without diabetes (Reutrakul & Mokhlesi, 2017). Further studies are required to clarify these findings. Exercise is thus a critical strategy for these sufferers.

Another notable result of concern within our study is the finding that the OSA group demonstrated relatively more time spent being sedentary compared to the CON group. It is well recognised that sedentary behaviour is a lifestyle risk factor for the promotion of obesity, chronic inflammation, and metabolic disorders (Smith, Doyle, Pascoe, Douglas, & Jorgensen, 2007). Igelstom et al. (2013) measured sedentary time by means of an accelerometer, questionnaire, and a logbook and found in their moderate to severe OSA cohort, that in those who were obese and on CPAP therapy, the average time spent sitting was 9 hours 55 minutes (accelerometer), 7 hours 51 minutes (questionnaire), and 8 hours 21 minutes (logbook). These figures surpassed those of the general population, where mean sedentary time was reported as being 5-6 hours according to self-reported values (Bauman et al. 2011), or 7 hours 39 minutes according to accelerometry-derived data (Ainsworth et al. 2011). In comparison, our OSA group averaged 10 hours 56 minutes for sedentary time, as derived from the sleep-diary, were also all on CPAP therapy and had a mean BMI that fell within the obese category. Interestingly our CON group also reported, as derived from the sleep-diary, more total sedentary hours per day than the general population, 9 hours 54 minutes, with a mean BMI falling within the overweight category.

With no significant difference between our groups for low physical activity measures, but present for relative sedentary behaviour, this contrast between low physical activity and high sedentary time nevertheless highlights the necessity of assessing physical activity and sedentary time as separate constructs. This proposal is supported by two cross-sectional studies and one prospective study that showed consistent positive associations between sedentary hours and OSA severity even after adjusting for levels of physical activity (Buman et al. 2015; Kline, Krafty, Mulukutla, & Hall, 2017; Liu et al. 2022).

The reasons for these differences noted in sedentary behaviour and the amount of moderate to vigorous intensity physical activity between the OSA and control group in our cohort are likely multifactorial. When considering possible skeletal muscle dysfunction as a likely contributing factor to these findings, various potential mechanisms have been proposed. Evidence suggests a direct link between adipocyte-derived inflammatory cytokines, and skeletal muscle dysfunction (Langen et al. 2002; Pellegrinelli et al. 2015). Although we did not

obtain measures on systemic inflammation in the current study, one might hypothesise that a greater pro-inflammatory state in the OSA participants, compared to the CON participants, could be altering skeletal muscle function to result in a greater muscle fatigability, and consequently, a lower total volume of daily physical activity, and particularly at higher intensities. Another potential mechanism linking OSA to lower levels of physical activity is the effect of hypoxia on skeletal muscle function, bearing in mind all these participants are on CPAP therapy. There is evidence to suggest that repeated exposure to hypoxia may alter the skeletal muscle fibre type composition, shifting from oxidative type I muscle fibres, to glycolytic type II muscle fibres (Carrera et al. 2004; Daulatzai, 2011; Petrof, Hendricks, & Pack, 1996; Smirne et al. 1991). Type I muscle fibres, due to their slow twitch and oxidative characteristics, are much more fatigue resistant, able to maintain sustained activation longer than type II, or fast twitch muscle fibres. Type II muscle fibres, which rely on glycolytic metabolic pathways, are much more fatigable. While the current study did not assess muscle fibre type, it is possible that individuals with OSA, who are therefore chronically exposed to states of hypoxia, may see a shift in muscle fibre type and function to a more enhanced fatigability, which in turn may result in OSA individuals shying away from more intense exercise as it is more fatiguing (Hargens, Martin, Strosnider, Giersch, & Womack, 2019). Whether continuous positive airway pressure therapy treatment would be sufficient to mitigate for these possible changes within the context of this study is uncertain. While not directly related to skeletal muscle, but rather the musculoskeletal system, the recognised link between gout and OSA may predispose an OSA individual to joint pain and hence decreased mobility. Gout, being a form of inflammatory arthritis caused by raised uric acid levels within the blood stream (hyperuricemia), which is in turn hypoxia associated, may result in debilitating joint inflammation and pain for those affected. However, this is unlikely to be a primary contributing factor within our cohort in view of our findings that despite a significantly higher prevalence of gout within our OSA cohort, no difference in pain parameters as per the SF36 scores were reported between groups.

Contrary to the above results, and other studies, Verwimp et al. (2013), indicated that 79% of their participants with moderate to severe OSA (on CPAP therapy) exceeded both the recommendations of health enhancing physical activity (150 minutes per week of moderate to vigorous physical activity) as well as physical activity for weight loss (300 minutes per week) (J. Verwimp, L. Ameye, & M. Bruyneel, 2013). The authors also noted that, amongst the OSA sufferers with prior low levels of physical activity, the risk of comorbid conditions was still present, including diabetes and hypercholesterolemia, which could not be completely ameliorated. Thus, despite their adequate physical activity levels, it cannot entirely prevent comorbid disease risk even when someone is on CPAP therapy. Thus, as it suggests within

our cohort, living with a chronic condition is not a “rate-limiting” factor with respect to being physically active.

As alluded to earlier, understanding the contributions of all the relevant factors to OSA severity is clearly compounded by the multifactorial nature of sleep apnoea. The available data in our study does not rule out a complex relationship whereby OSA, even when managed with CPAP therapy, is still associated with low levels of physical activity, perhaps due to OSA symptoms such as daytime sleepiness and fatigue or another yet identified reason. In a study by Pendharkar et al. (2011) continuous positive airway pressure therapy increased exercise tolerance in obese individuals with OSA (Pendharkar, Tsai, Eves, Ford, & Davidson, 2011). While our findings showed differences in physical activity between our OSA and control group despite CPAP therapy treatment, it is unclear whether there would be an even greater difference if OSA participants were not being treated. Ultimately, given the well-established positive effects that chronic exercise has on cardiometabolic risk through improving cardiorespiratory fitness, independently of weight loss, understanding why treated OSA patients are still relatively inactive is crucial to improving their risk for chronic diseases.

The most common symptom of OSA is excessive daytime sleepiness (Franklin & Lindberg, 2015). Within our cohort, the OSA group, who were on CPAP therapy, had significantly higher Epworth Sleepiness Scale scores than the control group, with one in three being classified as having excessive daytime sleepiness. Numerous randomized controlled trials have demonstrated a significant improvement in daytime sleepiness when such patients are effectively treated with CPAP therapy (Engleman et al. 1999; McDaid et al. 2009). While excessive daytime sleepiness was still identifiable in some of our OSA group, we are unable to determine whether their scores had improved since the introduction of CPAP therapy as we did not have access to these baseline results. Excessive daytime sleepiness can also be driven by other comorbid diseases. An associated systemic condition, such as thyroid dysfunction, i.e., hypothyroidism specifically, was reported by one fifth of our OSA participants. Thyroid dysfunction and OSA can co-occur as prevalent health problems of the adult population with some overlapping symptoms such as excessive daytime sleepiness (Bahammam, Sharif, Jammah, & BaHammam, 2011). Furthermore, both OSA and hypothyroidism, often present with higher levels of sedentary behaviour and lower levels of physical activity. Subclinical hypothyroidism was common among patients with OSA (Mete et al. 2013). Given the higher Epworth Sleepiness Scale scores of the OSA group, inciting more sleepiness, our OSA cohort may be trying to compensate by rising later. Despite very similar

bedtimes, the OSA group in this study had significantly later wake-up times compared to the control group. Another aspect for consideration might be related to their comorbidities and associated chronic medication use. CMD medication use has been reported to have an influence on sleep (Hermida, Ayala, Mojón, & Fernández, 2011; Surani, Brito, Surani, & Ghamande, 2015). It is however interesting to note that there were no significant differences in any of the other sleep parameters between the two groups. For example, both groups had very similar sleep efficiency values and sleep durations, which may support the positive effects of CPAP therapy compliance.

The excessive daytime sleepiness mentioned above, has the potential to negatively affect the OSA participants' daytime functioning as well as contribute to their lower physical activity levels. Contrarily, it has been shown that sleepiness does not appear to be a primary factor of high sedentary behaviour levels in the OSA population (De Sousa, Cercato, Mancini, & Halpern, 2008). Despite the fact that the Epworth Sleepiness Scale is widely used in OSA research, there is published research suggesting that obesity may also significantly impact excessive daytime sleepiness levels (Pahwa et al. 2012; Pamidi, Knutson, Ghods, & Mokhlesi, 2011; Slater, Pengo, Kosky, & Steier, 2013). As will be discussed below, our OSA cohort was considered obese. Hence, the higher levels of excessive daytime sleepiness in the OSA group, but similar sleep characteristics among the OSA and control group, may indicate that perhaps the sleepiness is causing the OSA participants to be more sedentary and or vice versa, but that perhaps this increased sleepiness is as a result of the obesity as opposed to the OSA in view of all participants being on CPAP therapy.

Similar to other studies (Shneerson, 2012; Tom et al. 2018), the OSA group in this study had a mean BMI that fell within the obese category (BMI 38kg/m²), while the control group was classified as overweight. Obesity is a well-known risk factor for OSA (Jehan et al. 2017), but weight gain may also be driven by OSA itself. Our observation of obesity combined with lower activity levels in the CPAP-treated OSA group, suggests that physical inactivity may be contributing to obesity. Therefore, it would appear to be of utmost importance to increase the physical activity levels of OSA sufferers, as their excessive weight may exacerbate the severity of their comorbidities.

In our study, both the total number of chronic conditions as well as the number of CMD specific conditions observed among the OSA population was significantly greater than in the control

group. These conditions included hypertension, T2DM, hypothyroidism, gout, as well as mood disorders. Our analysis found that independent of how sedentary or moderately active the participants are, those with OSA are still more likely to have a chronic condition. This finding suggests a stronger link between the chronic condition and OSA, rather than to a lack of physical activity. Nevertheless, since this is not true for vigorous intensity physical activity, it seems that vigorous physical activity is the key in terms of managing comorbidities associated with OSA. Hence, this provides some evidence for the need to consider including vigorous intensity physical activity in future exercise interventions.

Research has shown that OSA episodes cause a surge in systolic and diastolic blood pressures during sleep (Basile, 2002), which is one of the reasons why CPAP therapy is considered essential to the management of OSA treatment. However, similar to the observation that the CPAP-treated OSA participants in this study still had more obesity than the CON group, they were also still more likely to have hypertension. Thus, one might hypothesise that either CPAP therapy alone is unlikely to reverse hypertension in individuals living with OSA, and/or perhaps CPAP adherence needs to be considered as a contributing factor. Dissanayake et al. (2021) showed that the expected reduction of blood pressure by CPAP therapy is limited (Dissanayake et al. 2021). Further clinical trials showed that when CPAP therapy was compared with antihypertensive medications as treatment for hypertension in OSA patients, the effect of CPAP therapy was lower than that of antihypertensive medication (Javaheri, Gottlieb, & Quan, 2020). It should be noted, however, that trials that showed no long-term reductions in blood pressure in OSA patients treated with CPAP generally had worse CPAP therapy adherence, indicating that it still added clinical benefit (Craig et al. 2012; McEvoy et al. 2016). Even though the extent to which CPAP therapy reduces blood pressure may be limited, as little as a 2mmHg decrease in either diastolic or systolic blood pressure can lead to a marked reduction in cardiovascular events and mortality in patients with hypertension (Etehad et al. 2016). Therefore, there appears to be a need address hypertension in individuals living with OSA.

The positive effects of physical activity, especially higher intensity exercise, on blood pressure are well documented. Some of these promising effects of exercise following treadmill walking and cycle ergometer training include improvements in pulse wave velocity, systolic blood pressure, triglycerides, and lipid hydroperoxides (McNeilly et al. 2012). High-intensity training has been shown to reduce pulse wave velocity, systolic blood pressure, and waist

circumference (Way et al. 2020). This highlights the value of increasing physical activity as part of the management approach for OSA participants. High-intensity interval training (HIIT) has been explored as a potential exercise intervention even in very obese individuals (Batrakoulis & Fatouros, 2022), though with certain limitations. One challenge with very obese individuals is their reduced physical fitness and mobility, which can make high-intensity exercises more difficult to perform. Additionally, the risk of musculoskeletal injury may be higher in this population during intense physical activities. Regarding the limitations of vigorous exercise in morbidly obese individuals, it's important to consider factors such as joint stress, cardiovascular strain, and overall discomfort. These limitations can make sustained vigorous exercise difficult for some individuals, potentially reducing adherence to exercise programs.

All diagnosed hypertensive patients within our cohort (OSA and CON groups) were on an anti-hypertensive medication, with none of the individuals controlled by means of lifestyle interventions only. Their recorded mean daytime blood pressure results suggested participants were all well controlled on their respective treatments. In this current study, while there were no notable group differences between diastolic and mean arterial pressure, systolic blood pressure was significantly higher in the OSA group as compared to the control group. Shi et al. (2017) reported increases in night-time systolic blood pressure in OSA hypertensive patients. Dopp et al, (2007) also showed increases in systolic blood pressure variability in hypertensive OSA patients. This may provide one plausible explanation for OSA remaining a major risk determinant for cardiovascular diseases (Shi et al. 2017). Of clinical importance is the finding that the gold standard for OSA treatment, CPAP therapy, reduced apnoea's, thereby preventing intermittent arterial pressure surges, and restoring the 'normal' nocturnal "dipping" pattern, as well as having a modest beneficial effect on daytime blood pressure. These additional decreases in arterial pressure further contribute to the reduction in cardiovascular risk in OSA patients (Dopp, Reichmuth, & Morgan, 2007). While our OSA cohort were all on CPAP treatment, it is possible that the observed elevated systolic pressures were related to their higher BMI's, lower levels of physical activity and additional comorbidities. Alternatively, considering the higher daytime sleepiness in the OSA group, it is possible that some of these individuals were not optimally CPAP adherent. Poor adherence would limit the efficacy of the treatment on the restorative qualities of sleep, which may contribute to the persistence of higher systolic blood pressure. Since this is not something we were able to assess in the present study, future work should investigate CPAP compliance in treated OSA patients who continue to present with poor cardiometabolic risk profiles.

In addition to the higher prevalence of physical illnesses, the OSA group in the present study also reported more mood disorders than the Control group. In individuals with OSA, the prevalence of mood disorders may be as high as 63% (Saunamäki & Jehkonen, 2007). The coexistence of severe mood disorders and OSA may have a further negative impact on quality of life (Mitra et al. 2021) as well as contributing to minimal motivation with regards to participation in physical activity and hence increased sedentary lifestyle.

As observed, having a diagnosed comorbidity was however not associated with sedentary behaviour nor lower physical activity levels in the present study. It is therefore unlikely that the presence of any additional illness solely limits the OSA participants from being more physically active. Furthermore, as the OSA group did not report inferior levels of physical functioning or limitations due to physical health, energy levels or pain, the lower levels of physical activity may perhaps be exacerbated by poor self-esteem, lack of motivation or due to their size

Limitations

A limitation to this study is the relatively small sample size, which made sub-group comparisons difficult. Due to the cross-sectional nature of the study, predictions about the relationship between physical activity, sedentary behaviour, and BMI, should be cautioned. OSA participants are on CPAP and the majority use chronic medication, where these pharmaceutical treatments may have side effects that can mask other aspects of the disease. There are some speculations around potential consequences of low CPAP adherence, which information was unable to be obtained in this study. Furthermore, muscle fibre types and their effect on OSA individuals, were not investigated in this study. Additionally, the cut points of the accelerometry may result in misclassification of some individuals, specifically older adults who have different physical activity recommendations than young and middle-aged adults. Moreover, we did not consider the differences in physical activity and sedentary behaviour between week and weekend days. The ethnic, professional, or socioeconomic homogeneities of the study population may limit the generalisability of the current findings.

2.5 CONCLUSIONS

In summary, the main findings of this study included that despite the sleep of the CPAP-treated OSA participants being of similar quality to the control group, they still suffered from more

obesity and chronic conditions, including hypertension and T2DM and reported more daytime sleepiness than the Control group. In addition, they engaged in less objectively-measured moderate and vigorous intensity physical activity and more sedentary behaviour than the control participants. Despite differences in comorbidities and activity levels between the two groups, participants in both groups reported similar levels of perceived health and physical functioning or limitations due to physical health, lower energy, or pain. These descriptive observations suggest that increasing physical activity across the spectrum, from reducing sedentary activities and increasing vigorous intensity exercise among the OSA participants may be a justified target intervention to reduce their obesity and CMDs, and possibly improve their daytime sleepiness.

The regression analyses with pooled data from all participants show that even when accounting for measured habitual sedentary behaviour and physical activity, the OSA group has more obesity. This suggests that factors other than physical activity might be driving obesity among OSA sufferers on CPAP therapy. Regardless of group, lower levels of vigorous intensity physical activity were associated with more obesity among all participants, suggesting that increasing vigorous intensity physical activity would be one way in which obesity could be addressed in all participants. The OSA group was more likely to suffer from a chronic condition than the control group when accounting for absolute time spent in sedentary behaviour, but not the other activity parameters. This suggests that moderate and vigorous intensity exercise might mitigate the risk for chronic conditions, but not actual time spent in sedentary activities. Finally, the OSA participants were more likely to suffer from T2DM than the control group when accounting for sedentary behaviour and moderate intensity physical activity, but not when accounting for vigorous intensity activity. Thus, vigorous intensity exercise might be protective against T2DM for the OSA participants.

The lack of group-by-activity interaction effects indicate that living with OSA does not alter the nature of the relationship between activity behaviours and obesity or disease risk as measured in this study. Thus, although the OSA group was less active and had worse disease profiles than the control group, one might hypothesise that they stand to experience similar health gains as the control group with changes in their activity habits. Furthermore, it is noteworthy to mention that while these simple models, physical activity and group explained quite a lot of the variation in BMI and WC, there are variables that we did not measure which might be important to manage adiposity in these participants.

Taken together, these findings would suggest that physicians should continue to encourage OSA patients being treated with CPAP therapy to exercise and reduce sedentary behaviour, especially where there is comorbid symptomology of systemic inflammation, hypertension, obesity, or diabetes. Thus, future physical activity interventions in this cohort should target exercise at higher intensities while simultaneously reducing sedentary behaviours to optimise management of OSA-related comorbidities. A recent review by Boldens et al. (2018), evaluating the efficacy of exercise as a treatment for OSA, having identified from our study the lack of exercise at high intensities, it is therefore necessary to conduct a review identifying the nature of exercise programs determining the benefit of exercise at a higher intensity level.

CHAPTER 3:

THE NATURE AND EFFICACY OF EXERCISE INTERVENTIONS IN THE MANAGEMENT OF OBSTRUCTIVE SLEEP APNOEA: SYSTEMATIC REVIEW

3.1 INTRODUCTION

Obstructive sleep apnoea (OSA) is the second most common sleep disorder and the most common sleep-related breathing disorder. It is characterized by multiple apnoeic and hypopnoeic events, as well as respiratory effort-related arousals during sleep (Faith S. Luyster, Buysse, & Strollo, 2010; F. S. Luyster et al. 2012). Patients with untreated OSA have disturbed sleep, and typically present with excessive daytime sleepiness and dysfunction (Lal, Weaver, Bae, & Strohl, 2021). The current gold standard treatment of OSA is positive airway pressure (PAP), therapy mainly continuous (CPAP) (Spicuzza, Caruso, & Di Maria, 2015), designed to improve upper airway patency during sleep, thereby reducing the number of apnoeic and hypopnoeic events and improving sleep quality.

There is evidence to suggest that individuals with OSA are at a significantly greater risk for cardiovascular diseases (CVD) and metabolic disorders (Jean-Louis, Zizi, Clark, Brown, & McFarlane, 2008), and indeed many OSA patients are overweight or obese (Jean-Louis et al. 2008). A recent systematic review and meta-analysis found in addition to overweight / obesity, OSA patients also present as being relatively inactive compared to the general population (Monique Mendelson et al. 2018). Low levels of physical activity may contribute to obesity and cardiovascular disease risk within OSA patients and vice versa. Thus, among OSA patients, addressing physical inactivity and diet may reduce risk for comorbidities such as cardiometabolic diseases through weight management. Accordingly, many clinicians do incorporate behavioural changes targeted at weight loss (e.g., increased physical activity, reduced caloric intake) (Gharibeh & Mehra, 2010), avoidance of alcohol and sedatives (i.e., substances which may promote upper airway collapse during sleep) and modification of nocturnal positioning (to minimize upper airway collapse and laryngopharyngeal reflux) in their therapeutic approach to treating OSA and its comorbidities.

The efficacy of these lifestyle interventions, such as dietary and exercise programmes, as an adjunct therapy to reduce OSA severity and risk for comorbidities in adults, have however,

until relatively recently, received little attention in the literature. In a small pilot study, Norman et al (2000) evaluated the effects of a six-month supervised exercise training and dietary intervention aimed at weight loss, focusing on physical and subjective measures associated with OSA. Of the nine participants, who had mild to moderate OSA and were between 21-60 years of age, four were not on CPAP treatment while five were being treated with CPAP. This combination intervention in both treated and untreated individuals found significant decreases in apnoea hypopnoea index (AHI: 21.7 ± 9.0 events/h to 11.8 ± 6.8 events/h, $p=0.002$), weight (110.9 ± 12.0 kg to 104.7 ± 12.3 kg, $p<0.001$) and body mass index (BMI, 31.2 ± 4.6 kg/m² to 29.6 ± 4.4 kg/m², $p<0.001$) in six months (Norman et al. 2000). Andrade et al (2016) found in their systematic review, that independent of weight loss, predominantly aerobic exercise resulted in reduced OSA severity (as evidenced through a reduced AHI) and daytime sleepiness, with increases in sleep efficiency and maximum cardiometabolic fitness (as evidenced by higher maximum oxygen consumption) (F. M. Andrade & R. P. Pedrosa, 2016). Thus, there is promising evidence emerging to suggest that lifestyle interventions which combine physical activity and dietary changes in OSA patients may be an effective adjunct treatment strategy.

Two meta-analyses have reviewed the effect of exercise therapy alone in treating OSA, and while focusing on weight loss, they did not address diet (Aiello et al. 2016; I. H. Iftikhar, Kline, & Youngstedt, 2014). Aiello et al. (2016) evaluated studies with CPAP therapy usage and an AHI >5 events per hour, that included specific exercise programme characteristics (e.g., duration $\geq$ two months, session duration $\geq$ 30 min and frequency $\geq$ twice a week), and found no statistically significant effect on BMI (unstandardized mean difference: -0.05 , 95% confidence interval (CI): -0.04 to 0.28), but did report an AHI decrease of four events/h when compared to patients not receiving exercise treatment (odds ratio: 72.33 , 95% CI: 27.91 to 187.49) (Aiello et al. 2016). In the second meta-analysis, Iftikhar et al. (2014), who did not specify the frequency or duration of exercise programmes per se, reported no significant change in BMI (-1.37 ; 95% CI -2.81 to 0.07 ; $p = 0.06$, AHI of -6.27 events/h), but a 32% significant reduction in AHI from baseline in the intervention group. While a further separate analysis of the data from three randomized control trials showed an AHI reduction of 7 events/h (95% CI: -1.86 to -12.48 ; $p = 0.008$) in favour of the exercise groups. Furthermore, Iftikhar et al. (2014) showed that the exercise interventions also improved sleep efficiency by 8% and aerobic fitness (as measured by VO₂ peak) by 24.6% and reduced daytime sleepiness (as measured by the Epworth Sleepiness Scale) by 28%, all studies excluded data of those on CPAP usage with an AHI >5 events per hour.

While these findings are encouraging, further research related to the efficacy of exercise intervention programmes is needed to assess the most effective modalities to be introduced or added into the combined treatment strategies for a more holistic approach. Interventions that combined exercise and diet have been somewhat effective in reducing OSA severity (F. M. D. d. Andrade & R. P. Pedrosa, 2016; Norman et al. 2000), improving cardiorespiratory fitness (F. M. D. d. Andrade & R. P. Pedrosa, 2016), reducing BMI (Norman et al. 2000), and reducing sleepiness and improving sleep efficacy (F. M. D. d. Andrade & R. P. Pedrosa, 2016). While some emerging evidence supports combined treatment strategies for OSA patients with the aim of optimizing risk factor control and reducing long-term morbi-mortality (Monique Mendelson et al. 2018), it is not yet clear which components of an exercise programme are best suited to (i) reducing severity of OSA or (ii) reducing BMI or (iii) improving sleep or fitness, (iv) reducing comorbidity risk and severity and thus further investigation is needed.

3.1.1 Aims

Aim: To systematically review the nature and efficacy of exercise interventions in reducing OSA severity and CMD risk factors in patients with OSA.

Objective 1: To assess the efficacy of an exercise programme on reducing OSA severity, improving sleep, body composition and fitness in patients with OSA.

Objective 2: To identify key components of these exercise interventions (e.g., mode of exercise, duration, frequency, intensity) associated with improved health outcomes in OSA patients.

3.2 METHODS

3.2.1 Search strategy

The search strategy used in this review followed standardized procedures outlined in the Preferred Reporting Item for Systematic Review and Meta-Analysis (PRISMA) Statement. Systematic literature searches were conducted across three electronic databases: PubMed, Scopus, and ISI Web of Science. These databases were used to retrieve studies published up until 1 January 2023. All citation libraries in the Web of Science Core Collection were considered, including Science Citation Index Expanded, Social Sciences Citation Index, Arts and Humanities Citation Index and Emerging Sources Citation Index library indexes. The

following search terms were used: “sleep apnoea”, “sleep apnea” or “sleep disordered breathing” AND “exercise” or “physical activity”. Title, abstract and keyword fields were used for Scopus and topic fields were used for ISI Web of Science. The following search filters were applied to their respective database searches: Language: English; Publication Dates: up to and including January 2023; Species: Human; Document Type: Article; Source Type: Journal. The complete search strategies for each database are presented in Appendix 4.

3.2.2 Eligibility criteria

Original peer-reviewed research studies reporting on the efficacy of exercise interventions in OSA patients were considered for inclusion in the present review. Studies were included if they: (1) were original research studies, (2) used an experimental trial design (e.g., randomized controlled trial, observational or prospective cohort study), (3) had a sample of human adult participants (i.e. aged 18 years or older), (4) included both OSA participants (diagnosed $AHI \geq 5$) and controls ($AHI < 5$), (5) tested an exercise intervention, (6) reported on pre and post measures for AHI and measure of fitness (e.g. VO_2 peak) or body composition (e.g. BMI) or sleep (e.g. Epworth Sleepiness Scale score) and (7) were published in English. Studies were excluded if they (1) reported on patients with central sleep apnoea or (2) were conference abstracts, other published abstracts, and grey literature (e.g., reports, white papers, academic theses, or dissertations).

3.2.3 Study selection

The study selection process is illustrated in the PRISMA diagram in Figure 3.1. Initial identification and screening of titles and abstracts was performed by the candidate (myself). To assess eligibility criteria, the candidate and fellow student independently reviewed the full texts, with discrepancies being resolved by discussion and disputes being mediated by supervisors.

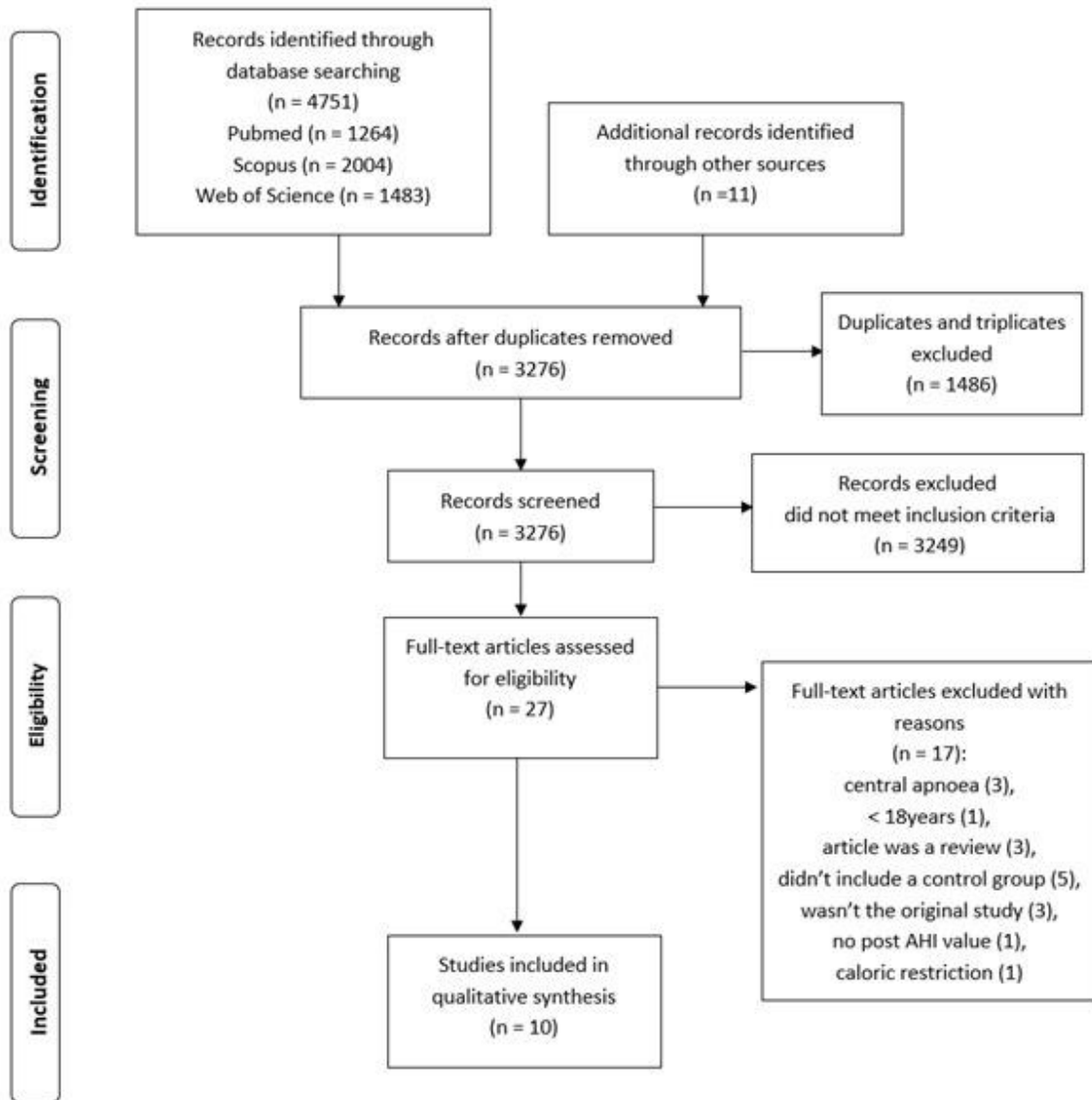


Figure 3.1: PRISMA diagram representing the data selection process.

3.3 RESULTS

3.3.1 Synthesis of evidence

The database search yielded a total of 4751 records, of which 1264 (27%) were extracted from PubMed; 2004 (42%) from Scopus; and 1483 (31%) from ISI Web of Science. An additional 11 records were identified through examining the reference lists of the studies initially identified through the databases. Of the 4762 identified records, 1486 duplicate records were removed, leaving 3276 records eligible for screening. Of these, 27 records were identified for full-text appraisal. A further 17 were excluded during the full-text appraisal process (reasons noted in Figure 3.1), leaving 10 records eligible for inclusion in the qualitative synthesis.

3.3.2 Study characteristics

3.3.2.1 Design and participants

The characteristics of the included studies are summarized in Table 3.1. All ten studies employed a randomized control trial design with one being a pilot study. Sample sizes of the included studies ranged from 20 (Sengul, Ozalevli, Oztura, Itil, & Baklan, 2011) to 96 participants (Berger et al. 2019), with cohorts spanning eight countries. Overall, the gender distribution of the studies was biased toward men; four studies contained only men participants (Berger et al. 2019; Jurado-García et al. 2020; Kline et al. 2012; Sengul et al. 2011), one study had only women participants (Bughin et al. 2020) and the other five reported on both men and women (da Silva et al. 2022; Desplan et al. 2014; Karlsen et al. 2017; Servantes et al. 2012; H. Yang, Liu, Zheng, Liu, & Mei, 2018). Mean ages of the participants ranged from 35 to 71 years of age. Participants in one study had chronic heart failure as well as OSA, diagnosed Class II–III, clinically stable for three months, ejection fraction <40%, peak VO₂ <20 ml/kg/min, stable and optimized medical therapy at least two months before the study, b-blocker therapy (Servantes et al. 2012).

Table 3.1: Methodological characteristics of the included studies.

Author, year	Study design	Population						Intervention				
		Country	Sample size	Gender	Age (y)	Exercise program	CPAP	Mode	Intensity	Frequency	Duration	Controls
Berger M, 2019	RCT	France	96	male	CG 62.0 (60.0-65.0) IG 62.0 (60.0-64.0)	aerobic and resistance training, and stretching	no current treatment for OSA	10min w/up 40min resistance and aerobic exercises (Nordic walking, aqua gym, gymnastics) 10min c/down stretches	VO ₂ peak	3x 60min/wk	9mo	standard diet and physical activity advice
Bughin F, 2020	RCT and PDS	France	64	female	CG 55.0 (10.3) IG 53.7 (9.9)	aerobic (1) and resistance (2) training, stretching, postural and balance exercises	no CPAP nor mandibular advancement devices	15min w/up 45min cycle ergometer 30min resistance 15min stretches. 15min postural and balance	moderate intensity: 1: 60% VO ₂ peak and 60% of 1RM 2. 2 sets, 8-10rep	3x120min/wk	2mo	education program
Da Silva R, 2022	RCT	Brazil	23	male (57%) and female (43%)	CG 72 ± 5 IG 71 ± 5.3	resistance training	CPAP use	15min w/up 1wk: 12-14rep x2 3wks: 12-14rep x3 4wks: 10-12rep x3 4wks: 8-10rep x3	maximum load repetitions until transient concentric failure	2x 60min/wk	3mo	Healthy lifestyle, including walking 3x20min/wk
Desplan M, 2014	Pilot RCT	France	22	male (59%) and female (41%)	35.0 - 70.0	aerobic and resistance training, stretching, postural and balance exercises	none of the participants were treated with CPAP or mandibular advancement devices	15min w/up 45min cycle ergometer 30min resistance 15min stretches. 15min posture and balance	55-65% VO ₂ peak	6x120min/wk	1mo	education program
Jurado-García A, 2020	RCT	Spain	68	male	CG 50.0 ± 9.5 IG 52.0 ± 6.6	aerobic training	no CPAP	5min w/up progressive walks 5min c/down	Session effort based on Borg RPE scale - w/up: 9-11 RPE exercise session: 11-14, 12-15 RPE c/down: 9-11 RPE	5x/wk: wk1 30min, wk2 40min, wk3 65min	6mo	usual physical activity monitored with a pedometer
Karlsen T, 2017	RCT	Norway	30	male (80%) and female (20%)	CG 49.9 ± 9.7 IG 52.5 ± 7.4	aerobic training (high intensity interval training)	CPAP use	10min w/up 4x4min treadmill walk or run intervals.	w/up at 70% HR _{max} treadmill run at 90-95% of HR _{max}	2x 30min/wk	3mo	regular physical activity self-determined

Kline CE, 2012	RCT	Columbia	43	male	CG 45.9 (2.2) IG 47.6 (1.3)	aerobic and resistance training	no CPAP use	3min walk between intervals aerobic: 50-150min treadmill (doesn't specify walk or run) Resistance: 2 set, 12 rep	aerobic: 60% of HRR moderate intensity	4x50-150min/wk 2x/wk (resistance)	3mo	by the control stretch 2x/w 60min
Sengul YS, 2011	RCT	Turkey	20	male	CG 48.0 (7.5) IG 54.4 (6.6)	aerobic training, resistance training and stretching	no CPAP	w/up (calisthenics, stretching, jog) ergometer, resistance, treadmill c/down (low temp walk, posture, stretch) c/down (low tempo walk, stretch)	Session effort based on modified Borg RPE scale- interval: 4-5 RPE	3x45-60min/wk 3x15-30min/wk	3mo	not advised or given any information or exercise
Servantes DM, 2012	RCT	Brazil	50	male (46%) and female (54%)	CG 53.0 ± 8.2 IG1 51.8 ± 9.8 IG2 50.8 ± 9.5	IG1: aerobic training IG2: aerobic and resistance training	no mention of CPAP use	IG1: 10min w/up 30-45min walking 10min c/down G2: 3 exercises for upper limbs, 4 exercises for lower limbs (x12-14-16)	aerobic: HR at anaerobic threshold, 10 heart rates down and 10 heart rates up, assessed by cardiopulmonary exercise testing. resistance: graduated free weights, 30-40% 1RM	3x45min/wk on non-consecutive days	3mo	untrained
Yang H, 2018	RCT	China	67	CG: 24 males (73%) /11 females IG: 22 males (69%) /10 females	CG 48.6 ± 7.2 IG 46.3 ± 6.4	aerobic training	rejection of CPAP therapy, nor surgical or mechanical ventilation treatment prior to inclusion	15min w/up 30min cycle ergometer 15min c/down	at anaerobic threshold	3x60min/wk	3mo	maintained previous lifestyle

Data are presented as mean ± standard deviation or median (interquartile range). AHI: apnoea hypopnoea index; BMI: body mass index; c/down: cool down; CG: control group; CPAP: continuous positive airway pressure; HR: heart rate; HRmax: maximum heart rate; HRR: heart rate reserve; IG: intervention group;

min: minutes; mo: month; OSA: obstructive sleep apnoea; PDS: project delivery system; RCT: randomized control trial; rep: repetitions; RM: repetition maximum; RPE: rating of perceived exertion; VO_2 : maximum oxygen consumption; w/up: warm up; wk: week.

3.3.2.2 Exercise interventions

The interventions comprised exercise programmes which were either face-to-face or home-based and made use of aerobic training, resistance training and or stretching / postural / balance exercises. The aerobic training programmes included cycling, walking, jogging and high intensity interval training (HIIT) and were mainly between 30 and 65 minutes in duration per session, with Kline's (2012) intervention including four 50-to-150-minute aerobic sessions on a treadmill. Resistance training programmes included aqua gym (a combination of aerobic and resistance training), weights and calisthenics and ranged from 30-60 minutes in duration per session. The stretching, postural and balance exercises, often prescribed in combination, were 10-30 minutes in duration per session. Four studies made use of aerobic, resistance and stretching / postural / balance exercises (Berger et al. 2019; Bughin et al. 2020; Desplan et al. 2014; Sengul et al. 2011), two studies used aerobic and resistance exercises (Kline et al. 2012; Servantes et al. 2012), three used only aerobic exercises (Jurado-García et al. 2020; Karlsen et al. 2017; H. Yang et al. 2018), and one used only resistance training (da Silva et al. 2022). With the exception of two studies (Kline et al. 2012; Singh & Bhardwaj, 2019), all the programmes included a 5–15-minute warm up session and five studies included a cool down session (5-15 minutes). The intensity of the aerobic exercise sessions were based on percentages of VO_2 peak (Berger et al. 2019; Bughin et al. 2020; Desplan et al. 2014), Borg's Rating of Perceived Exertion (RPE) scale (Jurado-García et al. 2020; Sengul et al. 2011), percentage of heart rate reserve (HRR) (Kline et al. 2012) or maximum heart rate (HRmax) (Karlsen et al. 2017) and anaerobic threshold (AT) (Servantes et al. 2012 Yang, Liu, Zheng, Liu, & Mei, 2018). The intensities of the resistance training sessions were based on one repetition maximum (1RM) values, maximum load repetitions until transient concentric failure (da Silva et al. 2022), and Borg's RPE scale (Jurado-García et al. 2020; Sengul et al. 2011),

The durations of the interventions ranged from one (Desplan et al. 2014) to nine months (Berger et al. 2019), with seven of the ten exercise interventions lasting three months. Participants attended between two (da Silva et al. 2022; Karlsen et al. 2017) and five (Jurado-García et al. 2020) sessions per week, with sessions durations ranging from 30 (Jurado-García et al. 2020; Karlsen et al. 2017) to 150 (Kline et al. 2012) minutes. The one-month intervention reported by Desplan et al (2014), comprised six two-hour sessions per week.

The control groups either received educational programmes (Berger et al. 2019; Bughin et al. 2020; Desplan et al. 2014), were asked to continue with their regular physical activity (Jurado-García et al. 2020; Karlsen et al. 2017), were given healthy lifestyle recommendations

including walking 20 minutes three times per week (da Silva et al. 2022), were given stretches to do twice a week (Kline et al. 2012), were given no information or programme (Sengul et al. 2011; Servantes et al. 2012), or were asked to maintain their previous lifestyle (Yang, Liu, Zheng, Liu, & Mei, 2018).

3.3.3. Study outcomes

3.3.3.1 Sleep parameters

Table 3.2 presents the main effects of the exercise interventions on sleep parameters in the included studies. AHI was considered the primary outcome measure in this analysis. While control groups exhibited varying responses over time, all intervention groups showed a decrease in AHI following their respective exercise regimes, with eight (80%) of the ten studies reporting a significant decrease in comparison to the control group (Berger et al. 2019; Bughin et al. 2020; Desplan et al. 2014; Karlsen et al. 2017; Kline et al. 2012; Sengul et al. 2011; Servantes et al. 2012; H. Yang et al. 2018). This finding was documented despite none of these eight studies being on CPAP treatment at the time of the interventions (Berger et al. 2019; Bughin et al. 2020; Desplan et al. 2014; Jurado-García et al. 2020; Kline et al. 2012; Sengul et al. 2011; Servantes et al. 2012; H. Yang et al. 2018). It is also interesting to note that the exercise interventions which resulted in “It should be noted that while most studies reported closely matched AHI baseline values for their control and intervention groups, there was one study (AHI reductions were primarily a combination of aerobic and resistance training, with only two effective studies consisting of aerobic training alone. The one-resistant training only programmes did not produce statistically significant reductions in AHI (da Silva et al. 2022). It should be noted that while most studies reported closely matched AHI baseline values for their control and intervention groups, there was one study (Karlsen et al. 2017) in which the AHI baseline value was significantly lower than that of the control group.

Oxygen desaturation index (ODI), defined as the number of arterial oxyhaemoglobin saturation drops by $\geq 4\%$ per hour of sleep, was measured in seven of the studies, of which none reported on CPAP. Three (30%) studies observed significant reductions in ODI in the intervention compared to the control groups, with all three of these studies implementing combined aerobic and resistance training programmes (Berger et al. 2019; Desplan et al. 2014; Kline et al. 2012). SpO₂ in turn is defined as the measurement of how much oxygen the blood is carrying as a percentage of its maximum carrying capacity. Mean SpO₂ during sleep was measured in seven studies (Berger et al. 2019; Bughin et al. 2020; da Silva et al. 2022;

Jurado-García et al. 2020; Karlsen et al. 2017; Sengul et al. 2011; H. Yang et al. 2018), resulting in a significant increase post the exercise interventions, with five of the seven studies not on CPAP therapy.

Three questionnaires were used to measure self-reported characteristics of sleep: the Epworth Sleepiness Scale (ESS), the Pittsburgh Sleep Quality Index (PSQI) and the Functional Outcome of Sleep Questionnaire (FOSQ). Of the studies that reported on ESS (Bughin et al. 2020; Desplan et al. 2014; Jurado-García et al. 2020; Kline et al. 2012; Sengul et al. 2011), two of the five (40%) observed significantly larger reductions in daytime sleepiness in the intervention compared to control groups (Bughin et al. 2020; Desplan et al. 2014). Only one study used the PSQI (Desplan et al. 2014), and observed a significant improvement in this self-reported measure of sleep quality in response to the intervention (100%). Two studies used the FOSQ (Jurado-García et al. 2020; Kline et al. 2012), and neither study (0%) noted differences in FOSQ scores between the intervention and control group over the course of the interventions. Sleep efficiency was defined as the total sleep time divided by the time-in-bed, expressed as a percentage. Three studies reported on sleep efficiency (Bughin et al. 2020; Sengul et al. 2011; Servantes et al. 2012), and only one of these three studies (30%) observed a significant improvement in sleep efficiency in response to the intervention (Servantes et al. 2012). All of these results were documented in studies reported not on CPAP therapy.

Table 3.2: Main effects of the exercise interventions on sleep parameters in the included studies.

Author, year		AHI (events/h)		ODI (events/h)		Mean SpO ₂ (%)		ESS score		PSQI score		FOSQ score		Sleep Efficiency (%)	
		PRE	POST	PRE	POST	PRE	POST	PRE	POST	PRE	POST	PRE	POST	PRE	POST
Berger, M. 2019	CG	21.0 ± 6.3	21.5 ± 10.0	22.0 ± 7.6	22.3 ± 10.7	92.4 ± 1.6	91.6 ± 1.7*	-	-	-	-	-	-	-	-
	IG	21.9 ± 7.0	16.8 ± 10.0*	21.4 ± 7.1	18.5 ± 10.8*	92.1 ± 1.3	91.9 ± 1.1	-	-	-	-	-	-	-	-
Bughin, F. 2020	CG	26.10 (15.8)	25.45 (18.0)	22.13 (22.8)	27.34 (15.6)	94.0 (2.0)	94.0 (2.0)	9.0 (7.0)	10.0 (8.0)	-	-	-	-	75.05 (21.62)	75.65 (15.39)
	IG	28.12 (12.9)	21.8 (17.3) *	22.3 (17.6)	14.9 (14.5)	94.0 (1.0)	95.0 (2.0)	10.0 (7.0)	8.0 (6.0) *	-	-	-	-	79.40 (16.78)	77.28 (16.94)
Da Silva, R. 2022	CG	29 ± 9	35.7 ± 6.7	-	-	94 ± 1	-	-	-	-	-	-	-	-	-
	IG	30 ± 7	26.4 ± 7	-	-	93 ± 4	-	-	-	-	-	-	-	-	-
Desplan, M. 2014	CG	39.8 ± 19.2	45.4 ± 22.5	24.9 ± 12.4	30.1 ± 23.1	-	-	8.0 ± 5.7	9.4 ± 5.8	8.0 ± 3.1	8.1 ± 3.8	-	-	-	-
	IG	40.6 ± 19.4	28.0 ± 19.3*	23.1 ± 15.8	17.6 ± 13.2*	-	-	13.6 ± 4.5	8.0 ± 5.7*	8.9 ± 3.1	6.2 ± 1.5*	-	-	-	-
Jurado-García, A. 2020	CG	27.0 ± 9.9	25.9 ± 16.3	25.0 ± 11.0	25.0 ± 15.4	94.0 ± 1.8	94.0 ± 1.9	9.8 ± 4.6	9.2 ± 3.9	-	-	32.0 ± 4.3	31.0 ± 4.5	-	-
	IG	29.0 ± 20.8	23.0 ± 13.1	33.0 ± 22.4	27.0 ± 18.9	93.0 ± 1.7	93.0 ± 2.5	9.9 ± 4.4	7.7 ± 4.5	-	-	32.0 ± 4.1	31.0 ± 4.1	-	-
Karlsen, T. 2017	CG	50.3 ± 25.5	50.3 ± 25.5	55.8 ± 28.6	-	91.6 ± 1.6	D	-	-	-	-	-	-	-	-
	IG	31.4 ± 21.7	23.9 ± 14.2*	36.9 ± 18.6	-	92.4 ± 1.6	D	-	-	-	-	-	-	-	-
Kline, CE. 2012	CG	24.4 (5.6)	28.9 (6.4)	16.8 (4.2)	23.2 (5.8)	-	-	7.3 (0.9)	7.9 (0.9)	-	-	16.0 (0.6)	16.0 (0.6)	-	-
	IG	32.2 (5.6)	24.6 (4.4) *	24.5 (4.2)	21.5 (3.7) *	-	-	11.1 (0.9)	8.7 (0.8)	-	-	15.1 (0.5)	16.7 (0.5)	-	-
Sengul, YS. 2011	CG	17.9 (6.5)	17.4 (11.2)	-	-	82.5 (5.4)	84.0 (4.5)	3.4 (5.07)	5.3 (4.2)	-	-	-	-	89.05 (5.96)	88.30 (9.53)
	IG	15.2 (5.4)	11.0 (5.3) *	-	-	83.9 (4.5)	83.6 (4.5)	8.2 (6.1)	7.0 (6.7)	-	-	-	-	80.58 (6.34)	86.35 (13.97)
	CG	22.8 ± 17.4	25.9 ± 18.8	-	-	-	-	-	-	-	-	-	-	75.9 ± 13.8	71.4 ± 15.9

Servantes, DM. 2012	IG	25.2 ± 24.7,	16.7±18.6*,	-	-	-	-	-	-	-	-	-	-	74.4 ±	79.6
		26.4 ± 17.6	16.4±11.1*											12.9	±11.9*
Yang, H. 2018	CG	19.5 ± 6.1	20.1 ± 7.0	12.4 ± 7.9	12.6 ± 5.8	97.0 ± 2.2	96.8 ±	-	-	-	-	-	-	77.6	83.2
	IG	20.2 ± 7.5	16.4 ± 5.2*	13.0 ± 8.2	11.4 ± 8.3	97.2 ± 2.4	2.3 97.5 ± 1.6*	-	-	-	-	-	-	±11.7	±10.1**

Data are presented as mean ± standard deviation or median (interquartile range). AHI: apnoea hypopnoea index; CG: control group; *d*: *difference*; *D*: *determined from graph*; ESS: Epworth Sleepiness Scale; FOSQ: Functional Outcomes of Sleep Questionnaire; IG: intervention group; ODI: oxygen desaturation index; PSQI: Pittsburgh Sleep Quality Index; SpO₂: percent saturation of oxygen in blood; * Statistically significant difference between the two groups in response to the intervention.

3.3.3.2 Body composition and fitness parameters

The main effects of the exercise interventions on body composition and fitness parameters of the included studies are presented in Tables 3.3 and 3.4 respectively. Of all the parameters measured (waist-to-hip ratio, weight, BMI, waist, and neck circumference), only BMI and neck circumference showed any significant change. Specifically, of the eight studies reporting on BMI (Berger et al. 2019; da Silva et al. 2022; Desplan et al. 2014; Jurado-García et al. 2020; Karlsen et al. 2017; Sengul et al. 2011; Servantes et al. 2012; H. Yang et al. 2018) (two on CPAP therapy), only two (25%) observed a significant reduction in BMI in response to the intervention (da Silva et al. 2022; Desplan et al. 2014). Five studies measured neck circumference (da Silva et al. 2022; Desplan et al. 2014; Jurado-García et al. 2020; Sengul et al. 2011; H. Yang et al. 2018) and only (20%) one observed a significant decrease in neck circumference in the IG following the intervention (Desplan et al. 2014).

Of the six studies which used aerobic training in their interventions, all six measured VO_2 peak as a marker of aerobic capacity. Of these five (83%) reported significant improvements in VO_2 peak in the intervention compared to the control groups over the course of the intervention, with only one on CPAP therapy (Berger et al. 2019; Desplan et al. 2014; Karlsen et al. 2017; Kline et al. 2012; Servantes et al. 2018). One metabolic equivalent (MET) is defined as the amount of oxygen consumed while sitting at rest and is equal to 3.5 ml O_2 per kg body weight per min. Both Desplan et al. (2014) and Sengul et al. (2011) measured MET values during resting state and aerobic exercises respectively and both (100%) showed a significant increase in MET values during these tasks, with neither on CPAP therapy. Furthermore, Desplan et al. (2014) indicates the OSA group are more inefficient with oxygen use, versus Sengul et al. (2011) whose OSA group had an improvement in aerobic capacity as they could exercise at a higher intensity compared to their control group, costing less effort for the same exercise which the control group cannot achieve. Finally, one study reported on FEV1/FVC% (proportion of vital capacity expired in one second of forced expiration to the full forced vital capacity). While not a traditional metric in the contexts of OSA or fitness, we present FEV1/FVC% as it potentially relates to airway resistance in people with OSA. The authors observed a small but significant improvement in this ratio in the intervention compared to the control group, indicating less pulmonary obstruction during the day (Sengul et al. 2011).

Table 3.3: Main effects of the exercise interventions on body composition in the included studies.

Authors, year		Waist-to-hip ratio		Weight (kg)		BMI (kg/m ²)		Waist circumference (cm)		Neck circumference (cm)	
		PRE	POST	PRE	POST	PRE	POST	PRE	POST	PRE	POST
Berger, M. 2019	CG	-	-	-	-	28.5 ± 4.5	28.7 ± 4.9	-	-	-	-
	IG	-	-	-	-	28.4 ± 4.3	28.3 ± 4.3	-	-	-	-
Bughin, F. 2020	CG	-	-	87.40 (11.90)	88.20 (9.60)	-	-	-	-	-	-
	IG	-	-	89.60 (13.40)	89.40 (11.50)	-	-	-	-	-	-
Da Silva, R. 2022	CG	-	-	-	-	29 ± 5.2	0.1 (-0.4 to 0.5)	100 ± 14.2	-	40 ± 3.7	-
	IG	-	-	-	-	27 ± 2.6	-0.4 (-0.2 to -0.7) *	96 ± 8.8	-	41 ± 4.4	-
Desplan, M. 2014	CG	-	-	-	-	31.3 ± 2.5	31.3 ± 2.2	104 (100–109)	104 (96–110)	41.0 ± 2.5	41.5 ± 3.0
	IG	-	-	-	-	29.9 ± 3.4	29.1 ± 3.1*	99 (96–104)	96 (93–102)	40.7 ± 3.5	39.2 ± 2.6*
Jurado- García, A. 2020	CG	0.93 ± 0.08	0.93 ± 0.08	-	-	32.0 ± 4.3	31.0 ± 4.5	-	-	40.8 ± 3.	39.8 ± 2.92
	IG	0.94 ± 0.06	0.94 ± 0.05	-	-	32.0 ± 4.1	31.0 ± 4.1	-	-	40.8 ± 3.61	39.8 ± 2.95
Karlsen, T. 2017	CG	-	-	118 ± 22	-	37.7 ± 4.8	-	-	-	-	-
	IG	-	-	121 ± 27	-	38.5 ± 7.0	-	-	-	-	-
Kline, C. E. 2012	CG	-	-	99.3 (5.1)	98.7 (5.0)	-	-	-	-	-	-
	IG	-	-	105.6 (3.0)	104.7 (3.1)	-	-	-	-	-	-
Sengul, Y. S. 2011	CG	0.96 (6.30)	0.96 (5.59)	-	-	28.4 (5.4)	28.3 (5.5)	103.5 (14.8)	101.3 (11.6)	41.30 (3.47)	41.60 (3.10)
	IG	0.97 (3.33)	0.97 (3.24)	-	-	29.8 (2.7)	29.2 (3.1)	104.3 (5.5)	104.5 (6.9)	41.15 (1.53)	42.15 (2.79)
Servantes, D. M. 2012	CG	-	-	-	-	26.9 ± 4.7, 28.0 ± 4.4	-	-	-	-	-
	IG	-	-	-	-	27.7 ± 3.7	-	-	-	-	-
Yang, H. 2018	CG	0.93 ± 0.08	0.92 ± 0.07	-	-	27.1 ± 3.5	26.8 ± 3.7	115.4 ± 16.7	111.6 ± 18.3	38.2 ± 4.1	39.1 ± 4.4
	IG	0.92 ± 0.07	0.91 ± 0.07	-	-	27.6 ± 4.7	24.5 ± 4.2	117.3 ± 18.4	115.2 ± 20.6	39.3 ± 5.6	37.4 ± 5.9

Data are presented as mean $\pm$ standard deviation or median (interquartile range). BMI: body mass index; CG: control group; IG: intervention group * Statistically significant difference between the two groups in response to the intervention.

Table 3.4: Main effects of the exercise interventions on fitness parameters in the included studies.

Author, year		VO ₂ peak (ml/min/kg)		MET (kcal/kg/min)		Power max (W)		FEV1/FVC (%)	
		PRE	POST	PRE	POST	PRE	POST	PRE	POST
Berger, M. 2019	CG	23.0 ± 6.0	23.4 ± 5.9	-	-	-	-	-	-
	IG	24.4 ± 6.0	26.7 ± 6.1*	-	-	-	-	-	-
Bughin, F. 2020	CG	-	-	-	-	-	-	-	-
	IG	-	-	-	-	-	-	-	-
Da Silva, R. 2022	CG	-	-	-	-	-	-	-	-
	IG	-	-	-	-	-	-	-	-
Desplan, M. 2014	CG	23.2 ± 6.0	19.8 ± 4.6	3.3 ± 1.7	2.91 ± 1.2	-	-	-	-
	IG	21.3 ± 5.6	22.9 ± 5.6*	3.6 ± 1.9	4.6 ± 1.0*	-	-	-	-
Jurado-García, A. 2020	CG	-	-	-	-	-	-	-	-
	IG	-	-	-	-	-	-	-	-
Karlsen, T. 2017	CG	27.0 ± 6.8	27.0 ± 5.1	-	-	-	-	-	-
	IG	28.2 ± 7.4	30.2 ± 7.7*	-	-	-	-	-	-
Kline, C. E. 2012	CG	-	-	-	-	-	-	-	-
	IG	-	-	-	-	-	-	-	-
Sengul, Y. S. 2011	CG	16.6 (4.87)	18.4 (3.5)	4.8 (1.4)	5.3 (1.0)	141.5 (35.9)	147.5 (25.5)	85.5 (4.9)	83.7 (4.7)
	IG	15.4 (3.6)	17.5 (5.6) *	4.4 (1.0)	5.4 (1.0) *	112.5 (35.5)	155.0 (18.1) *	77.0 (4.69)	78.80 (3.80) *
Servantes, D. M. 2012	CG	15.7 ± 3.0	12.8 ± 3.2*	-	-	-	-	-	-
	IG1	15.4 ± 2.7	20.6 ± 4.4*	-	-	-	-	-	-
	IG2	15.6 ± 2.7	20.9 ± 4.2*	-	-	-	-	-	-
Yang, H. 2018	CG	29.5 ± 6.7	29.4 ± 8.1	-	-	68.9 ± 8.4	69.1 ± 9.0	-	-
	IG	28.4 ± 7.1	32.1 ± 8.5	-	-	67.3 ± 9.1	70.4 ± 10.2	-	-

Data are presented as mean ± standard deviation or median (interquartile range). CG: control group; FEV1/FVC%: ratio measuring the amount of air exhaled in one second vs. the amount exhaled in a full breath; IG: intervention group; MET: metabolic equivalent of oxygen consumed at rest; VO₂: volume of oxygen consumption; * Statistically significant difference between the two groups in response to the intervention

3.4 DISCUSSION

This systematic review included ten RCTs which evaluated the efficacy of physical activity interventions on OSA severity, sleep, body composition and fitness parameters in participants diagnosed with moderate and severe OSA. Eight (80%) of the studies observed a significant effect in reducing the severity of OSA as evidenced by decreases in AHI, ranging from four to twelve events per hour (Berger et al. 2019; Bughin et al. 2020; Desplan et al. 2014; Karlsen et al. 2017; Kline et al. 2012; Sengul et al. 2011; Servantes et al. 2012; H. Yang et al. 2018.). These findings are similar to values reported in a meta-analysis by Lins-Filho et al. (2021), and work conducted by Mendelson et al. (2018) where exercise training resulted in a reduction of eight events per hour in AHI, but smaller than changes observed in studies measuring the response of AHI to CPAP therapy alone with a great decrease of 25.27 events per hour (Imran H Iftikhar et al. 2017). These improvements in AHI are also smaller than what has been reported in studies which induced weight loss in obese patients with OSA using diet alone, in which AHI reductions ranging from 16 to 23 have been reported (Anandam, Akinnusi, Kufel, Porhomayon, & El-Solh, 2013; Mitchell et al. 2014). However, the effect observed in the present systematic review following an exercise intervention remains clinically relevant since each one-unit increase in AHI has been associated with a 6% increase of stroke risk in mild-to-moderately severe OSA male patients (Redline et al. 2010). In addition, the OSA severity in the participants from three of these studies following the exercise intervention improved from severe to moderate (Desplan et al. 2014; Karlsen et al. 2017; Kline et al. 2012) and one from moderate to mild (Sengul et al. 2011). These findings are perhaps of added clinical value in view of the observation that nine of the studies included in this review were conducted on OSA patients not on CPAP therapy at the time of the intervention, therefore providing evidence of benefit despite the absence of the gold standard of treatment for OSA.

A common factor noted amongst the eight studies that reported a significant improvement in AHI (Berger et al. 2019; Bughin et al. 2020; Desplan et al. 2014; Karlsen et al. 2017; Kline et al. 2012; Sengul et al. 2011; Servantes et al. 2012; H. Yang et al. 2018), was that seven utilised a combination of aerobic and resistance training (Berger et al. 2019; Bughin et al. 2020; Desplan et al. 2014; Karlsen et al. 2017; Kline et al. 2012; Sengul et al. 2011; Servantes et al. 2012), with the remaining study using aerobic training alone (Yang, Liu, Zheng, Liu, &

Mei, 2018). Of the one study (Silva, Martinez, Bueno, & Uribe-Ramos, 2019) that only made use of resistance training interventions, three months in duration.

Of the eight studies (80%) that observed a reduction in AHI in the intervention group, five were conducted over a period of three months (Karlsen et al. 2017; Kline et al. 2012; Sengul et al. 2011; Servantes et al. 2012; H. Yang et al. 2018) and one over a nine-month period (Berger et al. 2019), all with moderate intensity exercise, except for Karlsen et al (2017), who were on CPAP therapy, conducted a high intensity interval programme. The remaining two studies implemented their exercise programmes over four-week and eight-week periods respectively (Bughin et al. 2020; Desplan et al. 2014). Interestingly Desplan et al. (2014) showed significant AHI changes after only four weeks of combined aerobic and resistance training, but in this intervention the physical activity sessions were two hours in duration for six days of the week. This may indicate that it is the total amount (time and sessions) of exercise that results in the positive changes rather than the duration of the intervention. Furthermore, the fact that the six-month aerobic training intervention of Jurado-Garcia et al. (2020) failed to improve AHI may be related to the lower intensity (walking) utilised or the absence of any resistance training. Therefore, a combination aerobic and resistance training over a shorter period may be just as effective in reducing AHI than over a longer period, provided that either intensity or total exposure to exercise is sufficient. In reality committing to six days of exercise per week over a longer time period may not be sustainable (Desplan et al. 2014), while perhaps the approach of Berger et al which encourages three one-hour sessions each week may be more feasible. The key to the success of any exercise intervention is sustainability to attain the benefits on other health-related aspects such as cardiometabolic measures and reduced systemic inflammation.

ODI was significantly impacted in the OSA intervention groups in three of the seven studies in which it was measured. Similar to the findings above, it is interesting to note that these three studies all performed resistance and aerobic exercises, and no CPAP therapy was included in the intervention (Berger et al. 2019; Desplan et al. 2014; Kline et al. 2012). This reduction in ODI adds a benefit for inflammation and parasympathetic systems, as well as the cardiometabolic risks and comorbidities, as ODI is a measure representing hypoxic burden which is well recognised as a risk factor for the development of cardiometabolic disease. ODI reduction benefits may include: decreased systemic inflammation, and sympathetic activation, and less sleep fragmentation (André et al. 2020). The interplay between intermittent hypoxia, increased systemic inflammation and sympathetic activation as well as the effects of sleep

fragmentation, are some of the factors considered to greatly contribute to the effects of OSA as a risk factor for poorer cardiometabolic health (Blekic, Bold, Mettay, & Bruyneel, 2022).

It was surprising that daytime sleepiness was only reduced significantly in two of the five studies (Bughin et al. 2020; Desplan et al. 2014) in which AHI improved in response to exercise training and ESS was measured. Interestingly, although Kline et al. (2012) did not observe a statistically larger reduction in ESS in their intervention group compared to the control group, the intervention group's change in ESS had a moderate effect size ($d=-0.67$) and was accompanied by significant decreases in fatigue and increases in vigour. Furthermore, while ESS did not improve in Sengul et al's, (2011) intervention group, baseline ESS was not considered to be particularly high. Of these two studies, Bughin et al's, (2020) prescribed programme was a two-month intervention, three times a week for 120 minutes per session, while Desplan et al. (2014) required six days a week for 120 minutes per session but over one month, with more frequent and concentrated sessions. Both these resistance and aerobic interventions had specific instructions for the prescribed intensity ranging from 50-65% of VO_2 peak, the only two studies in the review to utilise a percentage of VO_2 peak for this purpose, with similar effects on AHI reduction and daytime sleepiness improvements. Of the three studies that measured sleep efficiency, in which all three demonstrated improvements in AHI, only Servantes et al. (2012) reported a significant improvement in sleep efficiency in the only home-based intervention. It should be noted that the participants in this study also suffered from stable chronic heart failure.

Increases in cardiorespiratory fitness are often expected following an aerobic exercise intervention, particularly if the participants exhibited prior higher levels of sedentary behaviour. In five of the studies (Berger et al. 2019; Desplan et al. 2014; Karlsen et al. 2017; Sengul et al. 2011; Servantes et al. 2012) in the present review in which AHI improved in response to the exercise intervention, improvements in aerobic fitness (VO_2 peak) were also observed. It is interesting to note that out of these five studies, only participants in one study were using CPAP therapy (Karlsen, 2017). Thus, exercise alone is able to reduce OSA severity and improve fitness in the absence of CPAP therapy. Furthermore, CPAP therapy alone in the Control group of the Karlsen et al. (2017) study did not alter AHI, while CPAP with high intensity interval training reduced AHI and improved fitness.

Cardiorespiratory fitness, assessed by VO_2 peak, significantly increased in the intervention groups in five of the six studies in which it was measured (Berger et al. 2019; Desplan et al. 2014; Karlsen et al. 2017; Sengul et al. 2011; Servantes et al. 2012). Of these five studies only one study showed a significant reduction in BMI and neck circumference values (Desplan et al. 2014). This was particularly surprising in the case of Burger et al. whose aerobic and resistance training intervention spanned nine months. Desplan et al. (2014) included both an aerobic and resistance component, and despite participants not being on CPAP therapy, they showed a reduction in neck circumference through their exercise intervention. Da Silva et al. (2022) was the only study that showed a decreased AHI, along with a significantly improved BMI through individualized exercise training in patients with moderate to severe OSA, while on CPAP therapy following a resistance training programme only. It is important to note that even though there appears to be a relationship between body composition and OSA severity, other studies (Berger et al. 2019; Jurado-García et al. 2020; Sengul et al. 2011; Servantes et al. 2012; Singh & Bhardwaj, 2019; H. Yang et al. 2018), showed a decrease in AHI without a decrease in BMI, suggesting that additional factors induced following an exercise intervention may help reduce OSA symptom severity.

An acute bout of physical exercise stimulates sympathetic nervous system activity, while decreasing parasympathetic nervous system activity during exercise. This will initially result in an increased heart rate to support the metabolic demands of exercise, which will revert to normal when exercise ceases. Following exercise, the autonomic nervous system demonstrates a shift in activity such that sympathetic nervous system activity withdraws, and parasympathetic nervous system activity becomes dominant (White & Raven, 2014). Thus, over time, repeated exposure to exercise may help reduce the sympathetic activation overload experienced by OSA. Yang et al. (2018) reported an improvement in the AHI of OSA patients following their three-month aerobic exercise intervention, being the only value which was statistically significant. These findings suggested that the beneficial effects of exercise on parasympathetic tone might be partly responsible for improvement of AHI in OSA patients, but requires further investigation (Yang, Liu, Zheng, Liu, & Mei, 2018). This reduction in sympathetic activation may further impact not only AHI, but also play a role in the reduction of OSA-associated cardiometabolic and other comorbidities, via multiple mechanisms. This is supported by the findings of Norman et al. (2000) that showed that improvements occurred in MET levels of cardiometabolic fitness and resting blood pressures of the patients with mild to moderate OSA receiving aerobic exercise and diet programme for six months (Norman et al. 2000).

Despite not measuring post-intervention weight or BMI, Karlsen et al. (2017) further observed a decrease in serum leptin (a hormone predominantly made by adipose cells, its primary role being to regulate long term energy balance and more importantly signals satiety), following a HIIT intervention in the OSA population (Sanner, Kollhosser, Buechner, Zidek, & Tepel, 2004). An association between leptin and obesity in individuals with OSA, has previously been demonstrated (Ciriello, Moreau, Caverson, & Moranis, 2021). Therefore, while exercise might not result in significant improvements in body composition, it may contribute to improved regulation of leptin levels. Further studies are required to confirm this hypothesis.

An additional hypothesis on the mechanisms for the positive effect of exercise on AHI is based on the premise that exercise increases respiratory muscle recruitment, and hence it seems plausible that exercise might result in increased upper airway muscle activation to increase upper airway diameter, and reduce airway resistance, thereby decreasing airway obstruction during sleep. Sengul et al. (2011) for example, reported a small but significantly positive change across multiple physical fitness parameters measured including VO_2 peak, MET and percentage FEV1/FVC, a respiratory measure reflecting lung function and air flow during inspiration and expiration. While these findings may support the above hypothesis, the FEV1/FVC observation needs to be interpreted with caution given the small actual change (1.8%). Future studies looking at this metric are needed to better understand any possible clinical relevance of this respiratory parameter.

While body composition changes varied across the exercise interventions in this review, physical activity may lead to a reduction in adipose tissue, which is a known source of cytokines and contribute to increased systemic inflammation. Cytokines (particularly IL-1 β , IL-6, and TNF- α) are also thought to increase inflammation of the upper airway muscles by leukocytes infiltration and interstitial oedema (D. A. Dobrosielski et al. 2015), pathological changes which might exacerbate symptoms of OSA. However, ultra-sensitive C-reactive protein levels, used as a marker of systemic inflammation, were found to be normal in non-obese patients with OSA, and did not change following two months of aerobic exercise training, a finding that further highlights the complexity of the pathogenesis of OSA and the positive exercise effects documented (Cavagnoli et al. 2014). This again emphasizes the suggestion that physical activity may improve muscle tone of the upper airways, leading to less collapse of airways at night (Netzer et al. 1997). Finally, exercise training is supposed to

activate the musculo-venous pump, counteracting fluid accumulation in the legs during daytime and preventing nocturnal rostral fluid shift that contributes to the upper airway collapse during sleep (Kline, 2016; M. Mendelson et al. 2016; S. Redolfi et al. 2015).

In summary this systematic review demonstrates that exercise interventions consisting of aerobic-only and combined aerobic and resistance training, of varying duration, can reduce symptom severity of individuals with moderate to severe OSA, regardless of whether they are undergoing simultaneous CPAP therapy or not. Interestingly, these improvements in AHI do not seem to be related to changes in obesity, but perhaps rather to improvements in fitness parameters, and the effect of aerobic exercise in AHI and ODI reduction.

3.5 CONCLUSIONS

3.5.1 In summary

The systematic review evaluated the impact of exercise on obstructive sleep apnoea severity. Of the ten studies included in this systematic review, eight improved AHI (seven without CPAP therapy), and while only one of these was accompanied with an improvement in BMI, five were accompanied by improvements in fitness. This suggests that the efficacy of exercise interventions on OSA severity may be more related to changes in the cardiorespiratory system than body composition. With regards to duration, while positive changes were observed in as little as one month and up to as long as nine months, it appears that at least three exercise sessions per week are required, but that is if fewer sessions are to be prescribed, exercise intensity needs to be high, and that walking alone may not be sufficient to induce changes in AHI.

The present systematic review provides promising evidence in favour of interventions incorporating physical activity to reduce OSA severity, improve cardiometabolic fitness parameters, as well as BMI and neck circumference, especially in patients with moderate to severe OSA who are not being treated with CPAP. Improving physical activity levels should be considered as a key component in the management of patients with OSA. The optimal combination of aerobic training and resistance exercises could also be better defined to enhance the development of exercise programmes for OSA patients. However fewer studies looked at resistance training alone. In order to optimize risk factor control and reduce long-

term morbimortality, there is also a strong need for combined treatment strategies for OSA patients, such as aerobic programmes alongside the use of CPAP.

3.5.2 Limitations

Our systematic review had a limited number of studies, which limits the generalizability of the results. The interpretation of the current systematic review may also be limited by publication bias (i.e., probability of unreported studies). Another limitation was that since only studies published in English were included, it is possible that relevant studies published in other languages were excluded.

3.5.3 Future direction for studies

Future intervention studies in this field are encouraged to make use of standardised, validated measures to assess sleep, fitness, and body composition parameters, with all measures being made both before and after the intervention. To better understand the potential efficacy of exercise interventions on risk factors for comorbidities such as hypertension or diabetes, studies should also include measures for these risk factors. Future studies should also include identification and implementation of the optimal exercise programmes for OSA patients, designed to accompany CPAP therapy and reduce their risk for comorbidities. Lastly, there is a need for interventions over a longer period of time, to assess whether the positive effects remain.

CHAPTER 4: SUMMARY AND CONCLUSIONS

4.1 OVERVIEW AND SUMMARY OF MAIN FINDINGS

The purpose of this thesis was to investigate, characterise, and compare the habitual sleep, physical activity and CMD risk profiles of adults living with OSA on CPAP therapy to age- and gender-matched adults without OSA. Cardiometabolic disease (CMD) risk profiles of both groups were assessed utilising medical history questionnaires (diagnosed chronic conditions and medication use), anthropometry measures (BMI, WC, neck circumference) and physiological measures (resting blood pressure and heart rate), while wrist-worn accelerometry was used to objectively measure and compare habitual sleep habits, sedentary behaviours, and physical activity intensity levels between the two groups. Furthermore, associations between CMD risk and the physical activity parameters in all participants were also explored. The rationale for this research relates to the need to determine the effectiveness of exercise intervention programmes as part of combined treatment strategies for adults living with OSA for a more holistic approach, by optimizing risk factor control and reducing long-term morbi-mortality. It is not yet clear which components of an exercise programme are best suited to (i) reducing severity of OSA or (ii) reducing BMI in OSA individuals or (iii) improving sleep or fitness, (iv) improving associated comorbidities and risk, and thus further investigation is needed. Henceforth, this thesis set out to systematically review the nature and efficacy of exercise interventions in reducing OSA severity and obesity and improving sleep in patients with OSA, by assessing the efficacy of an exercise programme on reducing OSA severity, improving body composition parameters in patients with moderate to severe OSA, as well as identifying the key components of these exercise interventions (e.g., mode, duration, frequency, intensity of exercise) associated with improved health outcomes in these patients.

The observational study in this thesis confirms previous findings that individuals with OSA being treated with CPAP had similar sleep quality but more daytime sleepiness, obesity, and worse disease profiles than age and gender matched adults who did not suffer from OSA. Furthermore, the OSA participants in this study were less physically active than the controls. Regression analyses suggest that while factors other than physical activity might be driving higher obesity among OSA sufferers, it seems that moderate and vigorous intensity physical activity reduce the risk for comorbidities in general, while vigorous intensity activity protects against T2DM specifically. Given the lack of interaction effects between group and physical

activity parameters, this study provides promising evidence that despite their worse CMD profile, the nature of the relationship between physical activity and CMD parameters is similar among all participants. Thus, OSA participants stand to benefit similarly from a health perspective if exposed to an exercise intervention than control participants.

As evidenced from the systematic review, an exercise programme may be effective in reducing the severity of OSA in patients both being treated using CPAP or undergoing no additional treatment for OSA. Sessions lasting between 30 to 150 minutes two to six times a week, implemented for a minimum of four weeks, but with longer durations being preferable. Interventions including both aerobic exercise and resistance training showed beneficial effects in reducing OSA severity while the one study which only incorporated resistance training did not show such effects. Given the paucity of studies using only resistance training, however, it would be premature to conclude that resistance training has no role to play in reducing OSA severity. The greatest benefits of exercise training were observed on AHI reduction and improvements in cardiorespiratory fitness, regardless of whether or not participants were being treated with CPAP therapy.

4.2 INTERPRETATION AND IMPLICATIONS

These findings highlighted the intricate relationship between treated OSA, markers of obesity, higher levels of sedentary behaviour, less vigorous intensity exercise and associated cardiometabolic disease risk. The lower levels of vigorous physical activity, and higher levels of SB, among the OSA group, are consistent with the findings of the OSA group's higher BMI, WC, and neck circumference, suggesting that the OSA group needs to be more vigorously active, due to their higher adiposity measures. However, it was found that regardless of physical activity or SB levels in the OSA group, the driving force for these levels is perhaps due to the higher number of chronic conditions among the OSA group. Nevertheless, having diagnosed comorbidities neither limited physical activity nor increased SB (this is a good thing from an exercise prescription perspective - as there is no obstacle to the OSA individuals becoming more active). Despite differences in disease and physical activity between OSA and CON groups, no differences in their levels of general health were found on review of the SF36 findings, especially the self-report of no physical functioning or limitations, lowered energy or more pain, indicating the OSA groups lower levels of intense physical activity may be as a result of their excessive daytime sleepiness lethargy. Furthermore, reducing the SB time

among the OSA group may reduce their number and severity of associated comorbidities. Whilst even when treated with CPAP, adults with OSA are still more obese and have more CMD, strongly suggesting that a holistic approach including exercise (and diet) be considered to improve their management and ultimately improve their quality of life. These and the systematic review results further support that the treatment of OSA should include a physical activity component as part of routine care. Following the systematic review findings, perhaps the most effective exercise programme structured over a longer term (three to four months), with the duration of a minimum of 30 minutes per session, at least three times per week, focusing on both aerobic and resistance exercises. It was found that exercise can reduce the severity of OSA with limited changes in BMI, and improve cardiometabolic fitness, sleep quality, and excessive daytime sleepiness conditions.

4.3 FINAL REMARKS AND FUTURE DIRECTIONS

Given the ageing of the global population, and increasing prevalence of obesity and non-communicable diseases, OSA prevalence will likely continue increasing as observed over the past ten years. Hence there is a need for extending the life expectancy of the OSA sufferers, to not only live longer, but to experience an improved quality of life. Furthermore, this thesis showed recommendations for the importance of exercise as an adjunct therapy to CPAP. Whilst CPAP therapy reduces OSA severity and thereby ameliorates some of the cardiometabolic and chronic disease sequelae, despite treatment, there is still a strong association between individuals with OSA and obesity, hypertension, T2DM and other conditions. In addition, CPAP therapy is not available to all individuals with moderate to severe OSA. While the addition of physical activity may aid energy expenditure with subsequent cardiometabolic benefits, it is recognised that it will not treat OSA exclusively and would therefore be considered an adjunct therapy.

The economic constraints of the majority of the South African population have resulted in a reliance on the public healthcare system, which is resource-constrained for financial reasons, and access to CPAP devices for patients is limited. In addition, Roche et al. (2021) observed that the public healthcare system in South Africa does not routinely screen for OSA, and therefore there is 29% of the population with undiagnosed OSA. Physical activity opportunities are often restricted as a result of limited access to safe outdoor exercise spaces and affordable indoor gyms/clubs. Moreover, there is limited supervision by qualified professionals for those

with increased cardiometabolic and comorbid risks, particularly during physical activity. The development of effective public-private partnerships may go a long way in alleviating the challenges of OSA patients, in particular, the provision of financial assistance for CPAP devices, implantation of adjunct therapies, as well as public awareness educational campaigns.

Given the promising evidence base for the role of exercise, a need emerges for an exercise intervention that can be offered in the public health care system for OSA patients with limited resources. The findings from this study suggest that long-term, longer duration and an aerobic and resistance-based intervention needs to be considered in terms of the design of such a plan, and future studies would then need to assess feasibility and validity of such programmes.

While this study is adding to the evidence on the importance of healthy lifestyles (particularly more physical activity at higher intensities and less sedentary time) in the prevention and treatment of OSA and its comorbid conditions, clinicians should be aware of these links and make appropriate recommendations, such as healthy eating and regular exercise, to their patients. To provide more personalized strategies in the era of precision medicine, the associations of various healthy lifestyles with OSA outcomes need to be characterized in further detail, such as dose-response relationships and interactions with genetic predisposition.

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APPENDICES AND SUPPLEMENTARY DATA

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Appendix 1: Consent form



Physical activity and sedentary behaviour among patients with obstructive sleep apnoea in South Africa

PARTICIPANT INFORMATION SHEET

Why am I receiving this letter?

The University of Cape Town is conducting a research study comparing physical activity and sleep between adults with and without a sleep-related breathing disorder known as obstructive sleep apnoea. This study forms part of the research thesis component of MSc student Batsheva Brand. If you are interested in taking part in this study, please read further.

Why are we doing this study?

We know that sleep is very important for our health. In fact, we now know that people with sleep disorders are at higher risk for weight gain and obesity, high blood pressure and heart disease and the blood sugar disease known as diabetes. After insomnia, the second most common sleeping disorder is sleep apnoea. People who suffer from sleep apnoea stop breathing for short periods of time while they sleep because their throat closes up. They then gasp to breathe again, and this happens many times during the night. The odd thing about the disorder is that 8 out of 10 people with sleep apnoea do not know that they suffer from it. The problem with leaving the disorder untreated is that over time risk for high blood pressure and heart disease increases. People with sleep apnoea are also very sleepy during the daytime and sometimes find it hard to focus at work. While many studies around the world have been done to understand sleep apnoea better, hardly any have been done in South Africa.

The most common treatment for sleep apnoea is a special device known as CPAP – which helps support breathing at night. We also know that losing weight and doing more physical activity can help improve quality of life in patients with sleep apnoea. To better understand just how much South Africans with sleep apnoea might benefit from exercise, we first want to measure just how much physical activity these patients do during the day time. The aim of this study is to compare physical activity levels, sitting time and sleep patterns between adults with and without sleep apnoea.

Who is responsible for the information contained in this letter?

The persons responsible for this research study are Dr Caroline D'Alton and Dr Dale Rae, from the University of Cape Town (contact details below).

Who can take part in this sub-study?

We are looking for men and women aged between 18-65 years. Specifically, we are recruiting 30 people who have been diagnosed with moderate or severe obstructive sleep apnoea, and whose



sleep study has shown that they have an apnoea hypopnoea index of 15 or more. We are also wishing to recruit 30 people who do not suffer from sleep apnoea. All volunteers need to be able to move about freely on their own (that is, they do not rely on a cane, walking aid, wheelchair etc) – as we wish to measure how much you move about during your everyday life.

Principles concerning research: your rights

It is important that you read and understand the principles that apply to **all persons** who agree to participate in the research study described below:

1. Taking part in the study is always **entirely voluntary**.
2. **You will not benefit directly** from taking part in the study.
3. As a participant, **you will receive feedback** relating to your own physical activity and sleep habits that we measure in this study.
4. Your **privacy** and **anonymity** will be maintained at all times. Your name, surname, identification number and any personal identifying characteristics will remain entirely confidential.
5. You are **free to withdraw** from the study **at any time** without anyone objecting and without penalty or loss of any benefits to which you are otherwise entitled. The principal investigators may also decide to withdraw you from the study.

The following information will help you to make a decision about whether or not you wish to participate. Please discuss any questions you have about this research with the study staff.

If I choose to take part, what is expected of me?

We will ask you to visit the Division of Exercise Science and Sports Medicine at UCT on two **occasions** as follows:

Visit 1

During this visit, we will help you complete a questionnaire about your health, sleep and physical activity, work and home environment. We will measure your height, weight, waist and neck circumference as well as your resting blood pressure and heart rate. We will then give you a small watch to wear on your wrist for 7 days and nights. This watch will let us see your sleep patterns as well as how active you are in the daytime during your usual everyday life. While you wear this watch, we will also ask you to keep a diary to tell us about your physical activity, work and sleep habits. This visit will take no more than 1 hour. If you are in the control group and the information you provide when completing the sleep apnoea screening questionnaire suggests a moderate to high risk of perhaps suffering from undiagnosed OSA, you will be excluded from further participation and provided with a referral to a health care professional for further investigation and review if you so wish.



Visit 2

One week later, we will ask you to please return the watch and diary to us.

Are there any risks to me if I decide to take part?

There are no risks associated with completing the questionnaires. There are no risks associated with wearing the wrist watch to measure your physical activity and sleep. Sometimes the watch can feel a little uncomfortable at first, but we will show you how to adjust it to make it comfortable. We are aware that we are in the midst of the COVID-19 pandemic. Please be assured that all staff in our building are screened every day before coming to work and that the room that you will come to will be fully cleaned and sanitised. The same is true for the scale, height meter, blood pressure cuff and wrist watch. We will also ask that you have your temperature measured and respond to the COVID-19 screening questions as per our building and UCT protocol prior to visiting us. As part of the UCT and building protocol, the wearing of masks is currently mandatory prior to being permitted to enter the building. In this way, we are doing all that we can to minimise the risk of infection.

Are there any benefits to me if I decide to take part?

There are no direct benefits to you should you agree to take part in this research study. We will however compensate you for your time and travel (R200) and you will receive personal feedback relating to your sleep and physical activity habits.

What will happen to the information we collect?

We will use the information collected to learn about the relationships between sleep apnoea and health outcomes. Only the study staff assigned to this project will analyse the information (but without your name or any personal identifiers). The information collected will be stored for a period of up to 5 years and will only be used for the purposes of this study.

The results of this research study may be published in a scientific book (known as a journal) to help improve our knowledge of sleep health. We may also use the results to help appropriate authorities guide public health recommendations. You will not be identified by name or by any other identifying information in any publication or report about this research.

What if something goes wrong?

Should any injury occur, or should any untoward event happen while participating in this study, study staff and medical personnel will provide on-site emergency medical care.

This research study is covered by an insurance policy taken out by the University of Cape Town in case you suffer a bodily injury while taking part in the study. The insurer will pay for all reasonable medical costs required to treat your bodily injury, according to the SA Good Clinical Practice Guidelines 2006, which are based on the Association of the British Pharmaceutical Industry



Guidelines. The insurer will pay without you having to prove that the research was responsible for your bodily injury. You may ask the principal investigator for a copy of these guidelines.

If you are harmed and the insurer pays for the necessary medical costs, usually you will be asked to accept that insurance payment as full settlement of the claim for medical costs. However, accepting this offer of insurance cover does not mean you give up your right to make a separate claim for other losses based on negligence, in a South African court.

Freedom to withdraw and confidentiality:

Your participation in the study is entirely voluntary, and you may withdraw at any time without having to explain why you wish to do so. The principal investigator may also decide to withdraw you from the study if she decides this is best for you. It is also important for you to know that your name, and any personal identifying characteristics, will remain entirely confidential. Your information will be kept in a locked file, made available only to the researchers in the study.

If you have any questions about your participation in the study, feel free to contact the student investigator (Batsheva Brand) or the Principal Investigators (Dr Caroline D'Alton or Dr Dale Rae):

Ms Batsheva Brand, MSc student. Division of Exercise Science and Sports Medicine, Department of Human Biology, Faculty of Health Sciences, University of Cape Town. Phone: 076 926 3561. Email: brnbar001@myuct.ac.za

Dr Caroline D'Alton, Clinical Lecturer. Division of Exercise Science and Sports Medicine, Department of Human Biology, Faculty of Health Sciences, University of Cape Town. Phone: 021 6595644. Email: CL.Dalton@uct.ac.za

Dr. Dale Rae, Senior Researcher. Division of Exercise Science and Sports Medicine, Department of Human Biology, Faculty of Health Sciences, University of Cape Town. Phone: 021 650 4577. Email: dale.rae@uct.ac.za

Alternatively, you may contact the UCT Human Research Ethics Committee for any ethical concerns or queries about your rights and welfare related to taking part in this study:

Prof Marc Blockman, Chairperson of University of Cape Town's Human Research Ethics Committee, Faculty of Health Sciences, Room E52-24 Groote Schuur Hospital Old Main Building, Observatory 7925. Phone: 021 406-6338.



Physical activity and sedentary behaviour among patients with obstructive sleep apnoea in South Africa

CONSENT FORM

Participant ID: _____

I, the undersigned, have been fully informed about the study entitled “Physical activity and sedentary behaviour among patients with obstructive sleep apnoea in South Africa” to be conducted by researchers from the Division of Exercise Science and Sports Medicine within the Department of Human Biology, Faculty of Health Sciences at the University of Cape Town. I understand what is involved, including the risks and benefits of taking part. I have had the opportunity to ask all the questions that I have relating to the study.

I understand that:

- Taking part is **entirely voluntary**.
- I am **free to withdraw** from the study **at any time** without anyone objecting and without penalty or loss of any benefits to which I am otherwise entitled.
- I **will not directly benefit** from taking part in the study.
- I **may receive feedback on my physical activity and sleep habits** on completion of the study.
- If I am in the **control group**, and on completion of the sleep apnoea screening questionnaire the results suggest a moderate to high risk of perhaps suffering from undiagnosed OSA, I shall be excluded from further participation and provided with a referral to a health care professional for further investigation and review if I so wish.
- My **privacy** and **anonymity** will be maintained at all times. My name, surname, identification number and any personal identifying characteristics will remain entirely confidential.
- I understand that my consent here indicates that I am willing to participate in this research study as described above.
- I will receive a signed copy of this informed consent document.

Please tick the appropriate box:

- ☐ I agree to participate in this study.
- ☐ I do not agree to participate in this study.

(Signature: Participant) Date: _____

(Signature: Witness) Date: _____

Appendix 2: Questionnaire

Physical activity and sedentary behaviour among patients with obstructive sleep apnoea in South Africa

PARTICIPANT CONTACT INFORMATION

Participant code: _____ Date: _____

PARTICIPANT DETAILS

First name: _____

Surname: _____

Postal address: _____

_____ Code: _____

Email address: _____

Phone number (h): _____ Cell phone: _____

EMERGENCY CONTACT

Please give us the contact details of someone we may call in case of an emergency.

Name: _____ Relation: _____

Cell phone: _____ Landline: _____

Physical activity and sedentary behaviour among patients with obstructive sleep apnoea in South Africa

GENERAL QUESTIONNAIRE

Participant code: _____

Date: _____

PARTICIPANT DETAILS

Date of birth: _____ Age: _____

Gender: _____

MEDICAL HISTORY AND HEALTH

Do you currently suffer from **any chronic medical condition**? Yes ☐ No ☐

If **yes**, please list the condition(s):

Name of condition	Person who diagnosed	Date diagnosed

Do you currently use any **chronic medication(s)**? Yes ☐ No ☐

If **yes**, please list the medication(s):

Name of medication	Purpose	Years taken

Version 1 | Approved | 16 April 2021

Have you ever been **diagnosed** with **sleep apnoea**? Yes ☐ No ☐

If **yes**, please provide the following information:

When was the diagnosis made? _____ mm/yy

How was the diagnosis made? _____

What was your **apnoea/hypopnoea index**? _____ AHI

Are you currently being treated for **sleep apnoea**? Yes ☐ No ☐

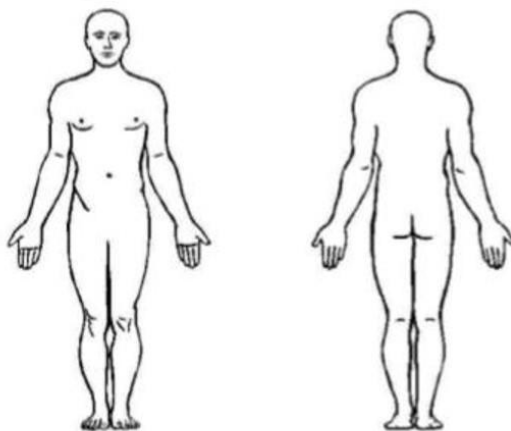
If **yes**, please describe your **treatment**: _____

Do you **snore loudly** (louder than talking or loud enough to be heard through closed doors)? Yes ☐ No ☐

Do you often feel **tired, fatigued, or sleepy** during the daytime, even after a "good" night's sleep? Yes ☐ No ☐

Has anyone has ever observed you **stop breathing** during your sleep? Yes ☐ No ☐

Please indicate on the figures below any aches, pains or problem areas.



Please give details of any areas indicated: _____

Are any of these injuries aggravated by exercise? Yes ☐ No ☐

Are you currently receiving treatment for any structural problem? Yes ☐ No ☐

If yes, please describe: _____

For women only:

Are you currently **pregnant** or have you **given birth** in the last 6 months? Yes ☐ No ☐

Are you currently breast feeding? Yes ☐ No ☐

Are you:

☐ Pre-menopausal

☐ Menopausal

☐ Post-menopausal

SF36 Questionnaire

INSTRUCTIONS

Please answer every question. Some questions may look like others, but each one is different. Please take the time to read and answer each question carefully by **circling** the number that best represents your response. Please respond to each line within each question.

1. In general, would you say your **health** is?

Excellent	Very Good	Good	Fair	Poor
1	2	3	4	5

2. Compared to one year ago, how would you rate your health in general **now**?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
1	2	3	4	5

3. The following questions are about **activities** you might do during a **typical day**. Does your **health** now **limit** you in these activities? If so, **how much**?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
A. Vigorous activities , such as running, lifting heavy objects participating in strenuous sports	1	2	3
B. Moderate activities , such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
C. Lifting or carrying groceries	1	2	3
D. Climbing several flights of stairs	1	2	3
E. Climbing one flight of stairs	1	2	3
F. Bending, kneeling, or stooping	1	2	3
G. Walking more than a mile	1	2	3
H. Walking several hundred yards	1	2	3
I. Walking one hundred yards	1	2	3
J. Bathing or dressing yourself	1	2	3

4. During the **past 4 weeks**, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your **physical health**?

	All the time	Most of the time	Some of the time	A little of the time	None of the time
A. Cut down on the amount of time you spend on work or other activities	1	2	3	4	5
B. Accomplished less than you would like	1	2	3	4	5
C. Were limited in the kind of work or other activities	1	2	3	4	5
D. Had difficulty performing the work or other activities (for example, it took extra effort)	1	2	3	4	5

5. During the **past 4 weeks**, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any **emotional problems** (such as feeling depressed or anxious)?

	All the time	Most of the time	Some of the time	A little of the time	None of the time
A. Cut down on the amount of time you spend on work or other activities	1	2	3	4	5
B. Accomplished less than you would like	1	2	3	4	5
C. Did work or activities less carefully than usual	1	2	3	4	5

6. During the **past 4 weeks**, to what extent has your **physical health** or **emotional problems** **interfered** with your **social activities** with family, friends, neighbours, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
1	2	3	4	5

7. How much **bodily pain** have you had during the **past 4 weeks**?

None	Very mild	Mild	Moderate	Severe	Very severe
1	2	3	4	5	6

8. During the **past 4 weeks**, how much did **pain interfere** with your **normal work** (including both work outside the home and housework)?

Not at all	Slightly	Moderately	Quite a bit	Extremely
1	2	3	4	5

9. These questions are about how you **feel** and how things have been with you during the **past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...

	All the time	Most of the time	Some of the time	A little of the time	None of the time
A. did you feel full of life?	1	2	3	4	5
B. have you been very nervous?	1	2	3	4	5
C. have you felt so down in the dumps nothing could cheer you up?	1	2	3	4	5
D. have you felt calm and peaceful?	1	2	3	4	5
E. did you have a lot of energy?	1	2	3	4	5
F. have you felt downhearted and depressed?	1	2	3	4	5
G. did you feel worn out?	1	2	3	4	5
H. have you been happy?	1	2	3	4	5
I. did you feel tired?	1	2	3	4	5

10. During the **past 4 weeks**, how much of the time has your **physical health** or **emotional problems interfered** with your **social** activities (like visiting friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
1	2	3	4	5

11. How **TRUE** or **FALSE** is each of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
A. I seem to get sick a little easier than other people	1	2	3	4	5
B. I am as healthy as anybody I know	1	2	3	4	5
C. I expect my health to get worse	1	2	3	4	5
D. My health is excellent	1	2	3	4	5

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PHYSICAL ACTIVITY

Do you **currently** (past month) participate in **regular physical activity**? Yes ☐ No ☐

If **yes**, please provide the following details:

What **type(s)** of exercise do you do in a usual week? _____

For how many **years** have you been exercising? _____ Years

On how many **days per week** do you exercise? _____ d/week

For how many **hours per week** do you exercise? _____ h/week

On a scale of 1 to 10, how would you rate the average **intensity** of your exercise sessions?

1 _____ 10

Intensity:	Very light	Moderate	Vigorous
Heart rate:	Low		Near max
Sensation:	"I could do this all day"		"I can't keep this up for long"

If you **do not currently** exercise, did you exercise in the past? Yes ☐ No ☐

If yes, please provide the following details:

How **long ago** did you stop exercising? _____ Years

Why did you **stop** exercising? _____

What **type(s)** of exercise did you used to do in a usual week? _____

On how many **days per week** did you used to exercise? _____ d/week

For how many **hours per week** did you used to exercise? _____ h/week

On a scale of 1 to 10, how would you rate the average **intensity** of your past exercise sessions?

1 _____ 10

Intensity:	Very light	Moderate	Vigorous
Heart rate:	Low		Near max
Sensation:	"I could do this all day"		"I can't keep this up for long"

Do you have any **condition or reason** for **not** being able to **move about** or **participate in physical activity** should you choose? Yes ☐ No ☐

If **yes**, please describe: _____

Do you need to make use of any **aid to move about** (e.g. cane, brace, wheelchair)?

Yes ☐ No ☐

If **yes**, please describe: _____

On a scale of 1 to 10, how **satisfied** are you with your current physical activity habits?

1 _____ 10

Satisfaction:	Not at all	Somewhat	Very
----------------------	------------	----------	------

What would you say are the **main barriers** preventing you from exercising? (you may choose more than one)

- ☐ Lack of facilities
- ☐ No motivation
- ☐ No time
- ☐ Injury/illness
- ☐ Unfit

- ☐ Appearance
- ☐ Lack of knowledge
- ☐ Family
- ☐ Work

OTHER LIFESTYLE FACTORS

On a scale of 1-10 (with 1 being poor and 10 being excellent), how would you assess the **quality** of your **eating habits**?

1 10

Quality:	Very poor	Moderate	Excellent
-----------------	-----------	----------	-----------

Which of these best describes your **smoking status** (any tobacco)?

- ☐ Smoker: Has smoked cigarettes regularly (at least 1 per day) for at least 1 year
- ☐ Occasional: Smokes, but not regularly
- ☐ Ex-smoker: Stopped for at least 1 year after smoking regularly
- ☐ Non-user: Never smoked regularly

If you are a **current smoker**, how **many** cigarettes do you smoke **per day**? _____ No/day

If you are an **ex-smoker**, how **many** cigarettes did you smoke **per day**? _____ No/day

Which of these best describes your **alcohol use**?

- ☐ Consumes alcohol: Has consumed alcohol (at least 1 per week) for at least 1 year
- ☐ Ex-consumer: Consumed alcohol in the past but has not used alcohol for at least 1 year
- ☐ Non-consumer: Has never consumed alcohol regularly

If you **currently consume alcohol**, how many **drinks** do you have in an average **week**?

_____ No/week

HOME ENVIRONMENT, EDUCATION AND OCCUPATION

How many people (adults and children) usually live in your home (including yourself)? _____

How **many rooms** does your home have this includes bedrooms, bathrooms, kitchen lounge etc)?
_____ No of rooms

Does the **household** or any member of the household (including yourself) **own or have** any of the following? (Include only if they are in working condition)

- | | |
|--|--|
| ☐ Electric iron | ☐ Sofa |
| ☐ Refrigerator | ☐ Radio or CD player |
| ☐ Television | ☐ Telephone(landline) |
| ☐ Satellite Dish or Cable Television | ☐ Cell phone |
| ☐ DVD player or VCR | ☐ Fan |
| ☐ Computer (only include a computer purchased by you or a member of your household) | ☐ Air conditioner |
| ☐ Mattress or bed | ☐ Bicycle |
| | ☐ Motorcycle |
| | ☐ Car or bakkie |

What is the highest grade you completed at school? _____ Grade completed

Have you completed any tertiary education (e.g. college, university)? Yes ☐ No ☐

How many years of formal education did you receive (including primary, secondary, tertiary / university but excluding pre-school/creche)? _____ Years formal education

What is your current employment status?

- | | |
|---|----------------------------------|
| ☐ Employed / self-employed – full time | ☐ Retired |
| ☐ Employed / self-employed – part time | ☐ Student |
| ☐ Unemployed | |

If you are employed:

How many **hours per week** do you work? _____ h/week

What time do you usually **start** work? _____ AM/PM

What time did you usually **end** work? _____ AM/PM

What best describes your **work schedule**?

- | | |
|---|---|
| ☐ Day shift only | ☐ Night shift only |
| ☐ Rotating shifts with night shifts | ☐ Irregular work hours |
| ☐ Rotating shifts with no night shifts | |

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Have you recently travelled abroad via plane?

Yes ☐

No ☐

If yes, What was your final destination? _____ (City, Country)

When did you arrive back in South Africa? _____ (Date home)

THE EPWORTH SLEEPINESS SCALE

INSTRUCTIONS

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired? This refers to your usual way of life in recent times. Even if you have not done some of these things recently, try to work out how they would have affected you. Use the following scale to choose the **most appropriate number** for each situation:

0 = would **never** doze

1 = **slight chance** of dozing

2 = **moderate chance** of dozing

3 = **high chance** of dozing

Situation	Score (0 – 3)
Sitting and reading	
Watching television	
Sitting inactive in a public place (e.g. theatre or meeting)	
As a passenger in a car for an hour with out a break	
Lying down to rest in the afternoon when circumstances permit	
Sitting and talking to someone	
Sitting quietly after a lunch without alcohol	
In a car, while stopped for a few minutes in the traffic	
TOTAL score	

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Appendix 3: Sleep and physical activity diary

ACTIVITY AND SLEEP DIARY		Participant ID code: _____						
COMPLETE BEFORE BEDTIME								
Start date:	Example day Monday PM	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Today was a work/ school / off / sick day:	Work							
What time and for how long did you nap or doze today?	17h30 20min							
Note any medication, supplements or drugs you took today: (e.g. over-the counter or prescription medications, recreational drugs, homeopathic formulations, vitamins)	Name: Panado Dose: 500mg Time: 13h35	Name: Dose: Time:	Name: Dose: Time:	Name: Dose: Time:	Name: Dose: Time:	Name: Dose: Time:	Name: Dose: Time:	Name: Dose: Time:
	Name: Multivitamin Dose: 1 caps Time: 07h00	Name: Dose: Time:	Name: Dose: Time:	Name: Dose: Time:	Name: Dose: Time:	Name: Dose: Time:	Name: Dose: Time:	Name: Dose: Time:
	Name: Dose: Time:	Name: Dose: Time:	Name: Dose: Time:	Name: Dose: Time:	Name: Dose: Time:	Name: Dose: Time:	Name: Dose: Time:	Name: Dose: Time:
Note any illness / symptoms you had today:	I had a cold and headache							
Note any physical activity or exercise session you did today (type, time, and intensity: easy, moderate, hard):	Walked the dog 06h30-07h00 (easy) Gym 18h30-19h30 (moderate)							

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COMPLETE IN THE MORNING								
	Example day Tuesday AM	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Last night, I got into bed at:	10pm							
Last night I tried to go to sleep at (lights out, eyes closed):	10:20pm							
Last night, it took me minutes to fall asleep :	±10min							
I woke up for the last time this morning at (eyes open, lights on):	6am							
How satisfied were you with your sleep?	☐ Not at all ☐ A little ☐ Somewhat ☐ Quite ☐ Very	☐ Not at all ☐ A little ☐ Somewhat ☐ Quite ☐ Very	☐ Not at all ☐ A little ☐ Somewhat ☐ Quite ☐ Very	☐ Not at all ☐ A little ☐ Somewhat ☐ Quite ☐ Very	☐ Not at all ☐ A little ☐ Somewhat ☐ Quite ☐ Very	☐ Not at all ☐ A little ☐ Somewhat ☐ Quite ☐ Very	☐ Not at all ☐ A little ☐ Somewhat ☐ Quite ☐ Very	☐ Not at all ☐ A little ☐ Somewhat ☐ Quite ☐ Very
How refreshed/ rested do you feel this morning?	☐ Not at all ☐ Slightly ☐ Somewhat ☐ Well- ☐ Very well-	☐ Not at all ☐ Slightly ☐ Somewhat ☐ Well- ☐ Very well-	☐ Not at all ☐ Slightly ☐ Somewhat ☐ Well- ☐ Very well-	☐ Not at all ☐ Slightly ☐ Somewhat ☐ Well- ☐ Very well-	☐ Not at all ☐ Slightly ☐ Somewhat ☐ Well- ☐ Very well-	☐ Not at all ☐ Slightly ☐ Somewhat ☐ Well- ☐ Very well-	☐ Not at all ☐ Slightly ☐ Somewhat ☐ Well- ☐ Very well-	☐ Not at all ☐ Slightly ☐ Somewhat ☐ Well- ☐ Very well-
Was this a typical night? (Yes or No)	Yes							

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FAQs and GENERAL INSTRUCTIONS

What is this Diary for? This diary is designed to gather information about your daily sleep and activity patterns and possible factors which might affect your sleep.

How often and when do I fill out the Diary? Please complete your diary every day for 7 days. The “Complete before bedtime” section should be completed before you go to bed at night.

The “Complete in the morning” section should be completed within one hour of getting out of bed in the morning.

What should I do if I miss a day? If you forget to fill in the Diary, leave the diary blank for that day.

What if something unusual affects my sleep or how I feel in the daytime? If you experience an unusual event (such as an illness, or an emergency) on a given day, you may wish to make brief notes in the “Additional Comments” section below.

Use the guide below to clarify what is being asked for each item of the Diary.

1. **Today was a work/ school / off / sick day:** Please note whether or not you worked or went to school/college/university today. Off-days may include weekend days, public holidays, sick days.
2. **What time and for how long did you nap or doze?** A nap is a time you decided to sleep during the day, whether in bed or not in bed. “Dozing” is a time you may have nodded off for a few minutes, without meaning to, such as while watching TV. Note all the times you napped or dozed from when you first got out of bed in the morning until you got into bed again at night. If you did not nap, write “N/A” (not applicable).
3. **Note any medication, supplements or drugs you took today** (e.g. over-the counter or prescription medications, recreational drugs, homeopathic formulations, vitamins): Record any over-the counter or prescription medications, recreational drugs, homeopathic formulations or vitamins/minerals that you used – whether usual or once-off. Record the name, dose and time you took each product today.
4. **Note any illness / symptoms you had today:** Please note down any illness and / or symptoms you experienced during this day. If you did not experience any illness/symptoms, write “N/A”.
5. **Note any exercise session you did today** (type, time): Record the type of exercise session you did today (e.g. walk, hike, yoga, gym, run, swim, tennis etc) as well as time-of-day you started and ended the session. If you did not exercise, write “N/A”.
6. **Last night, I got into bed at:** This is the time you physically get into bed, perhaps to read, but are not yet trying to sleep.
7. **Last night I tried to go to sleep at** (lights out, eyes closed): Record the time that you began “trying” to fall asleep (i.e. lights out and eyes closed).
8. **Last night, it took me minutes to fall asleep:** Beginning at the time you began trying to fall asleep, estimate how long it took you to fall asleep.
9. **I woke up for the last time this morning at** (eyes open, lights on): Record the time you woke up in the morning to begin your day (i.e. lights on and/or eyes open, you are no longer trying to sleep).
10. **How satisfied were you with your sleep?** Sleep “satisfaction” is your sense of whether your sleep was good or poor.
11. **How refreshed / rested did you feel when you woke up for the day?** This refers to how you felt after you were done sleeping for the night, during the first hour after you woke up.
12. **Was this a typical night** (Yes or No): Note whether this night was representative of what you usually experience.

ADDITIONAL COMMENTS (Please feel free to make additional notes about the week here):

Appendix 4: Systematic review search strategies by database.

(A) PUBMED	
1	"sleep apnoea [MeSH]" OR "sleep apnoea [tiab]" OR "sleep apnea [MeSH]" OR "sleep apnea [tiab]" OR "sleep disordered breathing [MeSH]" OR "sleep disordered breathing [tiab]" OR "sleep-disordered breathing [MeSH]" OR "sleep-disordered breathing [tiab]"
2	"exercise [MeSH]" OR "exercise [tiab]" OR "physical activity [MeSH]" OR "physical activity [tiab]"
3	#1 AND #2
4	Filter: Language - English
5	Filter: Species - Humans
6	Filter: Document type - Journal Article
(B) SCOPUS	
Filters:	Document type: Article Source type: Journal Language: English
1	TITLE-ABS-KEY ("sleep apnoea" OR "sleep apnea" OR "sleep disordered breathing" OR "sleep-disordered breathing")
2	TITLE-ABS-KEY ("exercise" OR "physical activity")
3	#1 AND #2
4	Limit to Language - English
5	Limit to Document type - Article
6	Limit to Source type - Journals
(C) ISI WEB OF SCIENCE	
Filters	Year: up until 2023 Document type: Article Keyword: Humans Language: English
1	TS=("sleep apnoea" OR "sleep apnea" OR "sleep disordered breathing" OR "sleep-disordered breathing")
2	TS=("exercise" OR "physical activity")
3	#1 AND #2
4	#1 AND #2 Restrict search to Language (English) and Document type (Article)

Appendix 5: Supplementary tables.

Table A2.1. Linear regression analyses looking at associations between BMI (dependent variable) and group with sedentary behaviour and physical activity (independent variables), including interaction terms, in all participants (n=37).

	Model 1 SB (%)	Model 2 MPA (%)	Model 3 VPA (%)	Model 4 SB (min/d)	Model 5 MPA (min/d)	Model 6 VPA (min/d)	Model 7 Diary-derived weekly PA duration (min/wk)
PA effect	0.09 (-0.22, 0.41), p=0.561	-0.34 (-0.99, 0.32), p=0.301	-0.76 (-1.68, 0.16), p=0.104	0.01 (-0.02, 0.04), p=0.457	-0.04 (-0.11, 0.04), p=0.310	-0.09 (-0.19, 0.01), p=0.087	-0.00 (-0.07, 0.06), p=0.910
Group effect	6.40 (-22.84, 35.64), p=0.659	10.31 (-3.39, 24.02), p=0.135	10.42 (2.10, 18.74), p=0.016	12.44 (-13.17, 38.05), p=0.330	11.23 (-2.68, 25.14), p=0.110	10.17 (1.78, 18.55), p=0.019	13.10 (6.17, 20.03), p<0.001
PA-by-group interaction effect	0.06 (-0.37, 0.50), p=0.774	-0.02 (-9.96, 0.93), p=0.971	-0.10 (-1.31, 1.11), p=0.870	-0.00 (-0.04, 0.04), p=0.900	-0.01 (-0.11, 0.09), p=0.823	-0.01 (-0.14, 0.12), p=0.889	-0.05 (-0.21, 0.10), p=0.470
Overall model	<i>F: 8.97,</i> <i>R²: 0.45,</i> <i>p<0.001</i>	<i>F: 9.47,</i> <i>R²: 0.46,</i> <i>p<0.001</i>	<i>F: 12.67,</i> <i>R²: 0.54,</i> <i>p<0.001</i>	<i>F: 8.74,</i> <i>R²: 0.44,</i> <i>p<0.001</i>	<i>F: 9.80,</i> <i>R²: 0.47,</i> <i>p<0.001</i>	<i>F: 13.34,</i> <i>R²: 0.55,</i> <i>p<0.001</i>	<i>F: 13.34</i> <i>R²: 0.55,</i> <i>p<0.001</i>

Data for the main and interaction effects are presented as beta coefficients with 95% confidence intervals. BMI: body mass index, SB: sedentary behaviour, MPA: moderate intensity physical activity, VPA: vigorous intensity physical activity, PA: physical activity.

Table A2.2. Linear regression analyses looking at associations between WC (dependent variable) and group with sedentary behaviour and physical activity (independent variables), including interaction terms, in all participants (n=37).

	Model 1 SB (%)	Model 2 MPA (%)	Model 3 VPA (%)	Model 4 SB (min/d)	Model 5 MPA (min/d)	Model 6 VPA (min/d)	Model 7 Diary-derived weekly PA duration (min/wk)
PA effect	0.21 (-0.45, 0.87), p=0.520	-0.61 (-2.03, 0.81), p=0.390	-1.07 (-3.12, 0.99), p=0.298	0.02 (-0.04, 0.09), p=0.449	-0.06 (-0.22, 0.85), p=0.373	-0.13 (-0.35, 0.97), p=0.257	0.02 (-0.12, 0.17), p=0.740
Group effect	-4.90 (-66.90, 57.09), p=0.873	25.95 (-3.86, 55.77), p=0.086	25.25 (6.67, 43.84), p=0.009	13.21 (-41.97, 68.39), p=0.629	27.57 (-2.54, 57.69), p=0.071	24.96 (6.26, 43.66), p=0.010	26.82 (11.53, 42.11), p<0.001
PA-by-group interaction effect	0.38 (-0.55, 1.30), p=0.413	-0.44 (-2.50, 1.61), p=0.662	-0.89 (-3.58, 1.81), p=0.509	-0.01 (-0.07, 0.10), p=0.763	-0.07 (-0.29, 0.15), p=0.547	-0.10 (-0.38, 0.19), p=0.503	-0.10 (-0.44, 0.23), p=0.532
Overall model	<i>F: 9.05,</i> <i>R²: 0.45,</i> <i>p<0.001</i>	<i>F: 8.52,</i> <i>R²: 0.44,</i> <i>p<0.001</i>	<i>F: 10.40,</i> <i>R²: 0.49,</i> <i>p<0.001</i>	<i>F: 8.20,</i> <i>R²: 0.43,</i> <i>p<0.001</i>	<i>F: 9.03,</i> <i>R²: 0.45,</i> <i>p<0.001</i>	<i>F: 11.09,</i> <i>R²: 0.50,</i> <i>p<0.001</i>	<i>F: 7.19</i> <i>R²: 0.40,</i> <i>p<0.001</i>

Data for the main and interaction effects are presented as beta co-efficients with 95% confidence intervals. WC: waist circumference, SB: sedentary behaviour, MPA: moderate intensity physical activity, VPA: vigorous intensity physical activity, PA: physical activity.

Table A2.3. Logistic regression analyses looking at associations between individuals diagnosed with chronic conditions (dependent variable) and group with sedentary behaviour and physical activity (independent variables), including interaction terms, in all participants (n=37).

	Model 1 SB (%)	Model 2 MPA (%)	Model 3 VPA (%)	Model 4 SB (min/d)	Model 5 MPA (min/d)	Model 6 VPA (min/d)	Model 7 Diary-derived weekly PA duration (min/wk)
PA effect	0.07 (-0.00, 0.15), p=0.062	-0.18 (-0.34, -0.02), p=0.028	-0.29 (-0.53, -0.05), p=0.018	0.01 (0.00, 0.01), p=0.034	-0.02 (-0.04, -0.00), p=0.030	-0.03 (-0.06, -0.01), p=0.015	-0.01 (-0.02, 0.01), p=0.385
Group effect	6.63 (-0.51, 13.77), p=0.068	-1.69 (-5.01, 1.63), p=0.307	-0.42 (-2.56, 1.72), p=0.692	7.02 (0.91, 13.13), p=0.026	-1.68 (-5.08, 1.73), p=0.323	-0.57 (-2.75, 1.60), p=0.597	0.26 (-1.42, 1.95), p=0.752
PA-by-group interaction effect	-0.08 (-0.19, 0.02), p=0.122	0.20 (-0.03, 0.43), p=0.080	0.26 (-0.05, 0.57), p=0.096	-0.01 (-0.02, 0.00), p=0.057	0.02 (-0.00, 0.05), p=0.095	0.03 (-0.00, 0.06), p=0.077	0.03 (-0.00, 0.07), p=0.075
Overall model	<i>F: 3.35,</i> <i>R²: 0.23,</i> <i>p=0.031</i>	<i>F: 3.94,</i> <i>R²: 0.26,</i> <i>p=0.017</i>	<i>F: 4.30,</i> <i>R²: 0.28,</i> <i>p=0.011</i>	<i>F: 3.86,</i> <i>R²: 0.26,</i> <i>p=0.018</i>	<i>F: 3.88,</i> <i>R²: 0.26,</i> <i>P=0.177</i>	<i>F: 4.48,</i> <i>R²: 0.29,</i> <i>P=0.010</i>	<i>F: 3.19</i> <i>R²: 0.22,</i> <i>p=0.037</i>

Data for the main and interaction effects are presented as odds ratio with 95% confidence intervals. SB: sedentary behaviour, MPA: moderate intensity physical activity, VPA: vigorous intensity physical activity, PA: physical activity.

Table A2.4. Logistic regression analyses looking at associations between individuals diagnosed with hypertension (dependent variable) and group with sedentary behaviour and physical activity (independent variables), including interaction terms, in all participants (n=37).

	Model 1 SB (%)	Model 2 MPA (%)	Model 3 VPA (%)	Model 4 SB (min/d)	Model 5 MPA (min/d)	Model 6 VPA (min/d)	Model 7 Diary-derived weekly PA duration (min/wk)
PA effect	1.08 (0.94, 1.22), p=0.270	0.80 (0.56, 1.13), p=0.206	0.63 (0.35, 1.13), p=0.117	1.01 (1.00, 1.02), p=0.256	0.98 (0.94,1.01), p=0.195	0.95 (0.89, 1.01), p=0.110	0.96 (0.89,1.03), p=0.236
Group effect	2957 (0.07, 1.3 ⁸), p=0.143	0.07 (0.00, 16.45), p=0.346	0.23 (0.01, 6.58), p=0.391	7178.19 (0.52, 9.9 ⁷), p=0.068	0.08 (0.00, 16.00), p=0.346	0.21 (0.01, 6.17), p=0.369	0.38 (0.03, 4.23), p=0.432
PA-by-group interaction effect	0.91 (0.77, 1.06), p=0.220	1.36 (0.91, 2.03), p=0.137	1.75 (0.93, 3.33), p=0.085	0.99 (0.97, 1.00), p=0.120	1.03 (0.99, 1.08), p=0.137	1.06 (0.99, 1.14), p=0.078	1.10 (1.00, 1.20), p=0.045
Overall model	<i>LR chi²: 6.57,</i> <i>p=0.087</i>	<i>LR chi²: 7.72,</i> <i>p=0.052</i>	<i>LR chi²: 9.26,</i> <i>p=0.026</i>	<i>LR chi²: 7.60,</i> <i>p=0.055</i>	<i>LR chi²: 7.64,</i> <i>p=0.054</i>	<i>LR chi²: 9.40,</i> <i>p=0.024</i>	<i>LR chi²: 12.66,</i> <i>p=0.005</i>

Data for the main and interaction effects are presented as odds ratio with 95% confidence intervals. SB: sedentary behaviour, MPA: moderate intensity physical activity, VPA: vigorous intensity physical activity, PA: physical activity.

Table A2.5. Logistic regression analyses looking at associations between individuals diagnosed with diabetes (dependent variable) and group with sedentary behaviour and physical activity (independent variables), including interaction terms, in all participants (n=37).

	Model 1 SB (%)	Model 2 MPA (%)	Model 3 VPA (%)	Model 4 SB (min/d)	Model 5 MPA (min/d)	Model 6 VPA (min/d)	Model 7 Diary-derived weekly PA duration (min/wk)
PA effect	0.92 (0.74, 1.14), p=0.423	1.09 (0.75, 1.60), p=0.643	0.72 (0.30, 1.75), p=0.465	0.99 (0.97, 1.01), p=0.412	1.01 (0.97,1.05), p=0.664	0.96 (0.88, 1.06), p=0.447	0.89 (0.68,1.17), p=0.398
Group effect	0.07 (1.08 ⁷ , 44775.3), p=0.696	33.84 (0.02, 62531.76), p=0.359	2.58 (0.02, 268.72), p=0.690	0.09 (4.87 ⁷ , 16891.46), p=0.698	31.22 (0.01, 75779.44), p=0.387	2.37 (0.02, 254.09), p=0.717	1.60 (0.07, 37.19), p=0.771
PA-by-group interaction effect	1.09 (0.86, 1.38), p=0.459	0.95 (0.62, 1.46), p=0.806	1.30 (0.52, 3.29), p=0.573	1.01 (0.98, 1.03), p=0.444	1.00 (0.95, 1.04), p=0.838	1.03 (0.93, 1.14), p=0.559	1.13 (0.86, 1.49), p=0.363
Overall model	<i>LR chi²: 7.49,</i> <i>p=0.058</i>	<i>LR chi²: 7.08,</i> <i>p=0.069</i>	<i>LR chi²: 7.70,</i> <i>p=0.053</i>	<i>LR chi²: 7.54,</i> <i>p=0.057</i>	<i>LR chi²: 7.09,</i> <i>p=0.069</i>	<i>LR chi²: 7.80,</i> <i>p=0.050</i>	<i>LR chi²: 8.86,</i> <i>p=0.031</i>

Data for the main and interaction effects are presented as odds ratio with 95% confidence intervals. SB: sedentary behaviour, MPA: moderate intensity physical activity, VPA: vigorous intensity physical activity, PA: physical activity.