Assessing effective treatments for Obstructive Sleep Apnoea (OSA) and exploring the relationships between OSA severity, eating behaviour and anxiety/depression in newly diagnosed adults with OSA

Ladan Ghazi

B.Sc. Nutrition Sciences, M.Sc. Public Health Nutrition

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Faculty of Medicine, Nursing and Health Science

Department of Nutrition, Dietetics and Food

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Abstract

Obstructive sleep apnoea (OSA) is a very common sleep-related breathing disorder and as the name suggests, is characterised by repetitive collapse of the upper airway during sleep. Importantly, untreated OSA is associated with a number of adverse consequences including cardiovascular disease, excessive sleepiness, anxiety, and depression. While there are a number of factors that increase the risk of an individual developing OSA, obesity is by far the largest independent factor. Thus, the majority of individuals diagnosed with OSA are obese. Furthermore, gaining additional weight is known to result in worsening of OSA symptoms. Current evidence suggests that lifestyle interventions (i.e. diet, exercise, or combination of the two) focusing on weight loss are strategies that assist patients with OSA in both (1) losing weight, and (2) reducing the severity of OSA and its associated symptoms. However, there is no robust evidence to clarify which of the lifestyle changes (i.e. changes in diet or in exercise or combination of the two) is the most effective intervention in adults with OSA.

Considering that OSA and obesity are strongly linked, it is of utmost importance to explore the underlying factors or mechanisms attributing to the link between OSA and obesity. Clarifying such underlying factors may help practitioners to provide more accurate and tailored advice when initiating treatment for patients with OSA. Depression and anxiety, which are the most common mental health issues associated with OSA, have also been reported to be attributed to weight gain and obesity. On the other hand, excessive fatigue and sleepiness, which are common symptoms in OSA, are suggested to result in alterations in eating behaviour and food intake. It is still unclear whether OSA severity itself is related to changes in eating behaviour. Moreover, there is a lack of robust evidence to explain whether obesity in OSA patients is a primary consequence of OSA or a secondary consequence of OSA-related symptoms (e.g., sleepiness, fatigue) or the conditions related to OSA (e.g., anxiety, depression).

The thesis is designed to fill a number of the current gaps in our knowledge and is presented in the four following chapters:

Chapter 1) A general literature review; providing current knowledge regarding OSA;
Chapter 2) A systematic review and meta-analysis; investigating effective treatments decreasing OSA severity [measured using the apnoea-hypopnoea index (AHI)];
Chapter 3) A cross-sectional study of the baseline data for The Sleeping Well Trial; evaluating the association between OSA severity, body mass index (BMI), eating behaviour, anxiety and depression symptoms in newly-diagnosed OSA patients;
Chapter 4) A general discussion; bringing results of the study together and concluding remarks.

Results from this work suggest that diet-based interventions (with or without exercise) are effective for improving OSA. While exercise interventions have been shown to improve upper airway muscle activity, they may not add additional benefit for reducing OSA severity or BMI. Except for the relationship between BMI and AHI, no strong relationships were found between OSA severity, age, gender, eating behaviour, and levels of anxiety and depression. The lack of strong associations in these findings suggests that there might be different underlying factors or other mechanisms attributing to the anxiety and depression levels, eating behaviour, and disease severity in patients with OSA, which were not detected with any of the measurement tools utilised.

Declaration

This thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

Ladan Ghazi

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List of Abbreviations

AASM	American academy of sleep medicine
AHI	apnoea hypopnoea index
BASE	be active sleep eat
BAI	Beck anxiety inventory
BDI	Beck depression inventory
BMI	body mass index
CPAP	continuous positive airway pressure
DEXA	dual-energy X-ray absorptiometry
DV	dependent variable
ESS	Epworth sleepiness scale
FOSQ	functional outcomes of sleep questionnaire
HADS	hospital anxiety and depression score
HREC	human research ethics committee
IPAQ	international physical activity questionnaire
ITT	intention to treat
IV	independent variable
LCD	low calorie diet
MH HREC	Monash Health human research ethics committee
NHMRC	National Health and Medical Research Council
NR	not reported
ODI	oxygen desaturation index
OSA	obstructive sleep apnoea
PSQI	Pittsburgh sleep quality index
QOL	quality of life
RCT	randomised controlled trial
SF	short form
T2DM	Type 2 Diabetes
TFEQ	three factor eating questionnaire
VLCD	very low calorie diet

Chapter 1: Introduction

1.1. What is obstructive sleep apnoea (OSA)?

Obstructive sleep apnoea (OSA) is a common sleep disorder characterised by repetitive collapse (apnoea) or partial collapse of the airway causing reduced airflow (hypopnoea) during sleep (2, 3). These airway obstructions are associated with falls in oxygen levels and sympathetic activation in the brain leading to increasingly powerful respiratory efforts until the airway re-opens and breathing is restored, often in association with an arousal from sleep (Figure 1) (4). These transient events also expose the sufferer to intermittent hypoxia and hypercapnia, large swings in intrathoracic pressure as well as surges in sympathetic activation, all of which have deleterious consequences on neurocognitive and daytime functioning as well as cardiovascular health (5, 6).

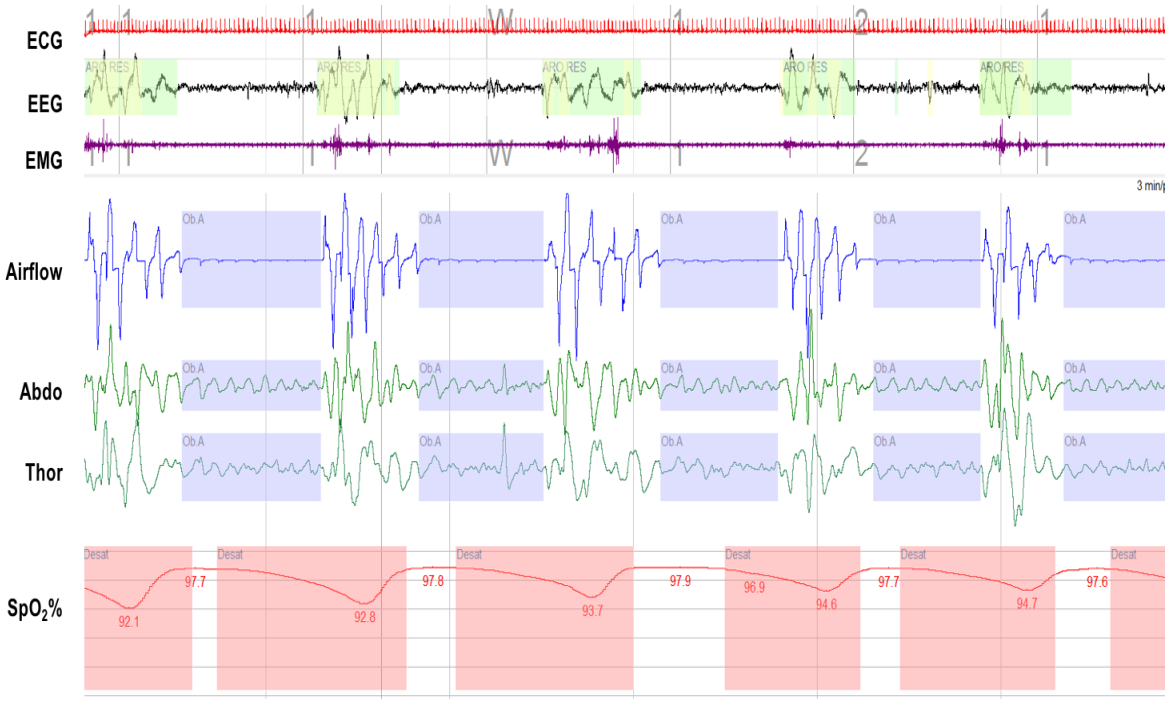


Figure 1. An example of the recorded signals during an overnight sleep study in a patient with severe OSA. This patient has repeated obstructive apnoea's (highlighted by the blue shaded boxes) indicated by the cessation of breathing in the airflow trace (i.e. flat line indicates zero flow) despite breathing efforts shown on the abdominal (Abdo) and thoracic (Thor) bands. The apnoea is associated with reductions in blood oxygen saturations (highlighted by the red shaded boxes on the SpO_2 trace) and is terminated when aroused from sleep (highlighted in green on the EEG). Abbreviations: SpO_2; peripheral capillary oxygen saturation, EEG; electroencephalogram.

1.2. OSA symptoms

OSA symptoms may vary between individuals. Some of the symptoms may occur during day, and others may occur at night-time. The majority of the OSA symptoms are usually recognised by the patients themselves. However, symptoms such as breathing pauses, gasping and snorting during sleep are mostly identified and reported by bed partners (Table 1) (7-12).

Daytime symptoms	Nocturnal symptoms
• Waking up fatigued/not well rested • Morning headache • Dry mouth and sore throat • Persistent daytime sleepiness • Chronic fatigue/lack of energy • Unintentional sleep episodes • Impaired cognitive performance • Short memory dysfunction • Confusion and difficulty in concentration • Decreased vigilance • Learning problems • Sexual dysfunction • High blood pressure • Irregular heart beat • Behavioural changes (e.g., irritability, anxiety and depression)	• Frequent and loud snoring • Witnessed interruptions in breathing • Chocking/gasping for air during sleep • Snorting during sleep • Restless sleep • Night-time sweating during sleep • Insomnia • Difficulty with sleep maintenance • Frequent tossing/turning during sleep • Nocturia • Nightmares • Unrefreshing sleep • Poor sleep quality

Table 1. Common symptoms of OSA, which may occur either at daytime or night-time.

1.3. Diagnosis of OSA

The diagnosis of OSA is often based on the combined findings from an overnight sleep study (often termed as polysomnogram), physical examination as well as detailed medical and family histories taken by the treating physician (13).

Polysomnography (PSG) is a non-invasive medical test most often conducted in a sleep clinic or hospital which helps a sleep specialist to identify the presence and severity of a variety of sleep disorders (e.g., OSA) (14). A polysomnogram involves recording brain activity, the oxygen levels in blood, eye movement, muscle activity, heart rate, and breathing while an

individual sleeps (15). The information gathered during the PSG will then be used for the diagnosis of OSA (16, 17). OSA is typically classified into three levels of severity based on the number of apnoeas and hypopnoeas that occur per hour of sleep, and is reported as the apnoea-hypopnoea index or AHI, and is detailed below in Table 2 (11, 15, 18).

AHI (number of events per hour)	OSA severity
<5	Normal
5-14	Mild
15-30	Moderate
>30	Severe

Table 2. Classification of OSA severity based on the AHI (number of apnoea and hypopnoea events per hour of sleep) according to the American Academy of Sleep Medicine (AASM) (15). Abbreviations: OSA; obstructive sleep apnoea, AHI; apnoea-hypopnoea index.

1.4. Prevalence of OSA

Given that the presence of OSA often remains largely undiagnosed in many individuals, the estimation of its true prevalence is difficult to report conclusively (8, 19). Nonetheless, various reports exist on the prevalence of OSA in different countries. However, the most recent systematic review of 24 studies (1980 – March 2016) conducted in Europe (n=14), North America (n=5), Australia and New Zealand (n=2), Latin America (1 study), East Asia (1 study) and South Asia (one study), demonstrated that the prevalence of OSA (defined as those with an AHI ≥5 events/hr) in the general population (aged > 18 years old) ranges from 9% to 38% (20).

1.5. What is the cause of OSA?

In order to have OSA, all patients have some degree of anatomical compromise of the upper-airway, which drives the propensity towards airway collapse. However, during wakefulness there is a compensatory negative pressure reflex that acts to increase the activity of the upper-airway dilator muscles and help maintain airway patency. By contrast, when an individual falls asleep, it typically results in the loss (or dramatic attenuation) of this negative pressure reflex and by extension, results in a decrease in activity of the dilator muscles. In an individual that already has a compromised anatomy, this often results in complete or partial airway collapse and an arousal from sleep is generally needed to stop the event (1).

Although the activity of the dilator muscle activity may increase as apnea progresses, the increases are generally insufficient to re-establish pharyngeal patency. Thus, the patient repeatedly arouses from sleep throughout the night and the cycle continues (Figure 2) (1).

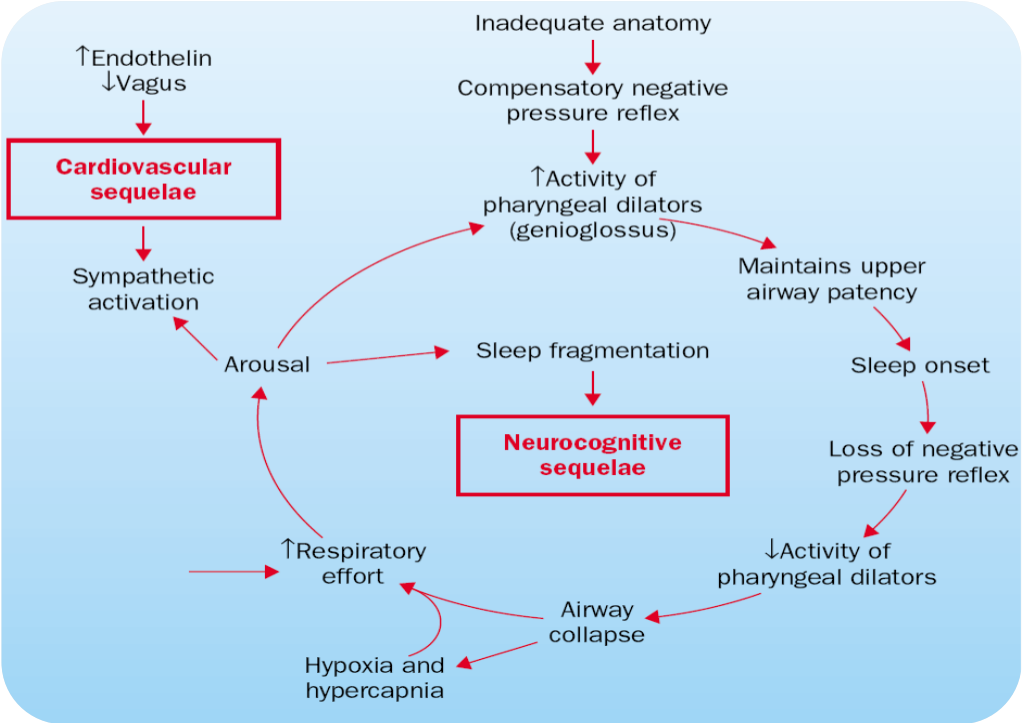


Figure 2. A demonstration of processes attributed to body anatomy and physiology, leading to the development of OSA and its associated cardiovascular and neurocognitive consequences (1).

1.6. Risk factors for OSA

To date, several risk factors for OSA have been identified which are presented in Table 3. The strongest risk factors comprise age, male gender and obesity (11, 21) – each of which is discussed in detail below.

1.6.1. Obesity

Of all the risk factors mentioned above, obesity is currently by far the largest independent factor associated with OSA (22). In fact, among those who have been diagnosed with OSA, 70 % were classified as obese (23, 24). Obesity and particularly central obesity (25) may attribute to the incidence of OSA through potential mechanisms including the aggravation of upper airway collapsibility and upper airway narrowing (26) which are both associated with alternations in balance between ventilatory drive and load (27), reduced lung volume and elevated lung elasticity (28). Given that obesity is the main risk factor for OSA (29) and its

epidemic is increasing worldwide (30, 31), it is estimated that a global incidence rate of OSA will also increase as a consequence (32).

Risk factors for OSA
• Overweight and obesity
• Male gender
• Advancing age
• Ethnicity (African-Americans, Pacific Islanders, Hispanics)
• History of tobacco use
• Use of alcohol
• Use of sedatives and muscle relaxants
• Menopause
• Enlarged tonsils
• Upper airway abnormalities
• Craniofacial abnormalities (e.g., small jaw)
• Large neck circumference (≥ 17 inches in men and ≥ 16 inches in women)

Table 3. Risk factors for OSA.

1.6.2. Gender

OSA is strongly associated with male gender (33). Sex-specific characteristics of males and females may differently contribute in predisposing two genders to OSA. It is suggested that increased vulnerability of males in developing OSA may be due to a greater collapsibility, length and resistance of their upper airway along with male-oriented pharyngeal-tissue properties (34). On the other hand, reduced prevalence and severity of OSA in females was suggested to be attributed from a female-oriented patterns for body fat distribution around hips, buttocks and thighs (35). Nevertheless, men have been more likely to distribute excess fat on the abdominal area and neck which may contribute to elevated mechanical load on their upper airway (35).

While males possess a greater risk of developing OSA, the importance of gender difference in predisposing individuals to OSA decreases with increasing age, regardless of their gender (36). Thus, postmenopausal females and males (over the of 50 years) appear to be at an equal risk for developing OSA (36).

1.6.3. Age

Several large cohort studies have clearly demonstrated that the prevalence of OSA increases with age, irrespective of an individual's gender (11, 37). However, the frequency and severity of OSA symptoms tend to decrease in both genders with age (specifically after 60-65 years) (38-40). Several studies have reported that increasing BMI in elderly adults has a smaller effect on OSA severity compared to middle-aged individuals (36, 41-43).

In an attempt to understand the increased prevalence of OSA in elderly adults, several studies have examined the underlying mechanisms leading to OSA, which can change with age. Advancing age in healthy subjects was accompanied by reductions in tone of the upper airway muscles and increased pharyngeal collapsibility during sleep (44), findings which have also been shown in patients with OSA (45). Moreover, several age-related factors including alternations in body structures surrounding the pharynx, enhanced deposition of fat in the para-pharyngeal area, and lengthening of the soft palate and tongue may also contribute to the worsening of upper airway collapsibility and therefore predisposition towards OSA with age (11, 46).

1.6.4. Ethnicity

Different ethnic groups exhibit different physical characteristics that may expose them to a greater vulnerability toward developing OSA. Ethnic differences in body traits such as craniofacial features and soft/hard tissue factors (e.g., tonsillar hypertrophy and inferiorly positioned hyoid bone) may alter mechanical properties of the upper airway and promote the occurrence of OSA or enhance its severity (11, 47-50).

The majority of the current OSA prevalence studies have been conducted in European countries (i.e., Caucasian population) and very limited information from other regions of the world (e.g., Africa and Latin America) is available (20). In addition, the results drawn from available studies are not easily comparable due to the inconsistent methods utilised in diagnosing OSA and its severity (51, 52). However, a few studies could be found which have compared the prevalence rate of OSA in different ethnic groups. One study demonstrated a greater prevalence of OSA among African-Americans (>65 years of age) compared to their Caucasian counterparts (53) after adjusting for potential confounders (i.e., BMI, age and gender). Moreover, those of Asian descent showed (a) a higher prevalence of OSA (54) as well as (b) an increased OSA severity (49, 55) compared to white Europeans, despite of the same level of obesity in both groups. The current evidence therefore suggests that a number of non-obesity related risk factors in Asians (e.g., differences in facial dimensions and other craniofacial features) may contribute to the greater prevalence of OSA in Asian populations (56, 57).

1.6.5. Alcohol use and smoking

The risk of developing OSA significantly increases with alcohol consumption and smoking (31, 58, 59). Alcohol exacerbates OSA and its associated nocturnal desaturation via ability to decrease upper airway muscle activity and therefore worsen airway patency (60, 61). Smoking interacts with sleep quality through increasing sleep fragmentation, inducing difficulties in falling asleep, interfering with sleep stability and imposing daytime sleepiness (62). Interestingly, smokers have showed an enhanced risk of snoring and OSA when compared with a group of non-smokers and former smokers adjusting for BMI, gender, age, and number of alcoholic drinks consumed per week (63). Specifically, the likelihood of smokers diagnosed with OSA was 2.5 times greater than former- smokers and non-smokers combined (63). Proposed mechanisms for how smoking may either predispose towards OSA, or worsen existing OSA (58) have suggested that smoking may (a) increase upper airway collapsibility during sleep potentially via the airway inflammation induced by smoke inhalation (64), (b) cause alternations in sleep architecture including a shift toward lighter stages of sleep following a longer latency to sleep onset (65), and (c) lead to relaxation of the upper airway muscles (caused by nicotine) (66).

1.7. Adverse consequences associated with OSA

There are several adverse consequences associated with OSA (11) which impose a substantial economic burden to society (67, 68). In Australia, the financial burden of OSA is approximately $2-8 billion annually (69, 70) which is comprised of both direct and indirect healthcare costs. The most common consequences associated with OSA are listed below:

1.7.1. Cardiovascular disease

The repetitive obstructions that occur during sleep in OSA patients may lead to the persistent elevation of blood pressure in this population (71-73). Such elevation in blood pressure occurring in relation to an underlying medical condition such as OSA is called secondary hypertension. According to the hypertension management guidelines (e.g., JNC VII and ESH-ESC 2007 recommendations), OSA is a major cause of secondary hypertension (74, 75). Secondary hypertension in OSA patients contributes to or exacerbates chronic health-threatening conditions including cardiovascular diseases, heart failure, and stroke (76-79).

Untreated OSA has been suggested to increase risk of cardiovascular death and likelihood of hospitalisation for heart failure (80). Also, OSA has been identified as an independent risk factor for stroke and all-cause mortality in large population studies (81-83). Anti-hypertensive treatment in OSA patients may not easily reduce their blood pressure without the management of OSA. Nevertheless, successful treatment of OSA has been suggested to have a great impact on blood pressure reduction. Inconsistencies in the a) baseline blood pressure, b) baseline OSA severity, and c) duration of OSA treatment in the current evidence (84-87), makes it difficult to identify to what extent OSA management controls/prevents hypertension.

However, reduction in blood pressure is very likely to contribute to the decrease in adverse cardiovascular events.

1.7.2. Metabolic syndrome

Metabolic syndrome is a compilation of cardiovascular and metabolic risk factors, characterised by obesity, insulin resistance, dyslipidaemia (abnormal increase in blood lipids), and hypertension (88) which increases the risk of cardiovascular disease, diabetes mellitus type 2 (T2DM) and all-cause mortality (89, 90). One of the widely used criteria for diagnosing metabolic syndrome is the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) definition (91). The NCEP ATP III guidelines (92) suggest that metabolic syndrome is present if three or more of the following five criteria are met:

1. Waist circumference >40 inches (men) or >35 inches (women)
2. Blood pressure >130/85 mmHg
3. Fasting triglyceride level >150 mg/dl
4. Fasting high-density lipoprotein cholesterol level <40 mg/dl (men) or <50 mg/dl (women)

Fasting blood sugar >100 mg/dl

Metabolic syndrome and OSA both occur in presence of the same conditions, namely increased amount of visceral fat and insulin resistance (93). However, Calvin et al. (94) suggested that OSA is associated with insulin resistance independent of obesity.

1.7.3. Neurocognitive impairment

Excessive daytime sleepiness (95), mental health issues (96, 97), motor vehicle accidents (98) and reduced work productivity (99, 100) are common neurocognitive consequences associated with OSA. Excessive daytime sleepiness in OSA patients can result in impaired performance in a number of cognitive domains including reasoning, attention, vigilance, all of which adversely affect quality of life in this population (101, 102).

If left untreated, OSA may result in unexpected costs and irreparable damage to one's health and safety. Untreated OSA among middle-aged workforce population may reduce employees' productivity and increase direct and indirect medical expenses, as well as costs of absenteeism from the workplace (103-105). Reduction in vigilance and attention could be fatal in some job categories such as drivers and operators of dangerous machines. Untreated OSA patients are at a two- to seven-times increased risk of being involved in motor vehicle accidents (100, 106).

Depression and anxiety are the most common mental health issues associated with OSA (107, 108) (and will be discussed in greater depth in section 1.8.2). However, it is still unclear whether depression is a primary consequence of OSA or a secondary consequence of OSA-

related symptoms (e.g., sleepiness, fatigue, and social withdrawal) or to the conditions related to OSA (e.g., obesity, hypertension) (107, 108).

1.8. Strong links between OSA, obesity and mental health issues

Given the strong links between OSA, obesity and mental health disorders (e.g., anxiety and depression) there has been an intense research effort in trying to understand how these factors are linked. Below is summary of what is currently known, and where the gaps in our understanding lie.

1.8.1. Obesity

Obesity results from a complex interaction of genetic, environmental, nutritional, and metabolic factors (109-112). In most of the cases, body weight increases when energy derived from food (calories eaten) exceeds energy expenditure (calories burned) (Figure 3). Energy expenditure is the sum of the energy (calories) that the body consumes when inactive, plus the energy used to digest and absorb food, added to the energy expended in physical activity. In order to reduce body weight, it is necessary to either decrease the energy intake or increase the energy expended in physical activity (113).

1.8.1.1. Defining obesity

Body mass index (BMI) is the most widely used metric in determining obesity and classifies individuals based on their height/weight characteristics (114). To calculate BMI, the weight of the individual in kilograms is divided by the individuals height in meters squared (kg/m^2) (115).

The current World Health Organisation (WHO) classification defines overweight as having a BMI between 25 and 29.9 kg/m^2 and obesity as having a BMI equal or greater than 30 kg/m^2 (116) (Table 4). However, some ethnic groups (e.g., Asian and Pacific population) may have an elevated risk for health-threatening conditions such as OSA, T2DM, and cardiovascular diseases, despite possessing a BMI ≤25 kg/m^2 (117-119). Moreover, some ethnic populations may store greater amount of body fat for the same level of BMI (e.g., Asian Americans versus whites) (120), while exhibiting significant lower rates of obesity compared to the other ethnic groups (121). Thus, to facilitate international comparisons, different cut-off points are recommended for reporting the prevalence of obesity in different ethnic groups (117, 118, 122).

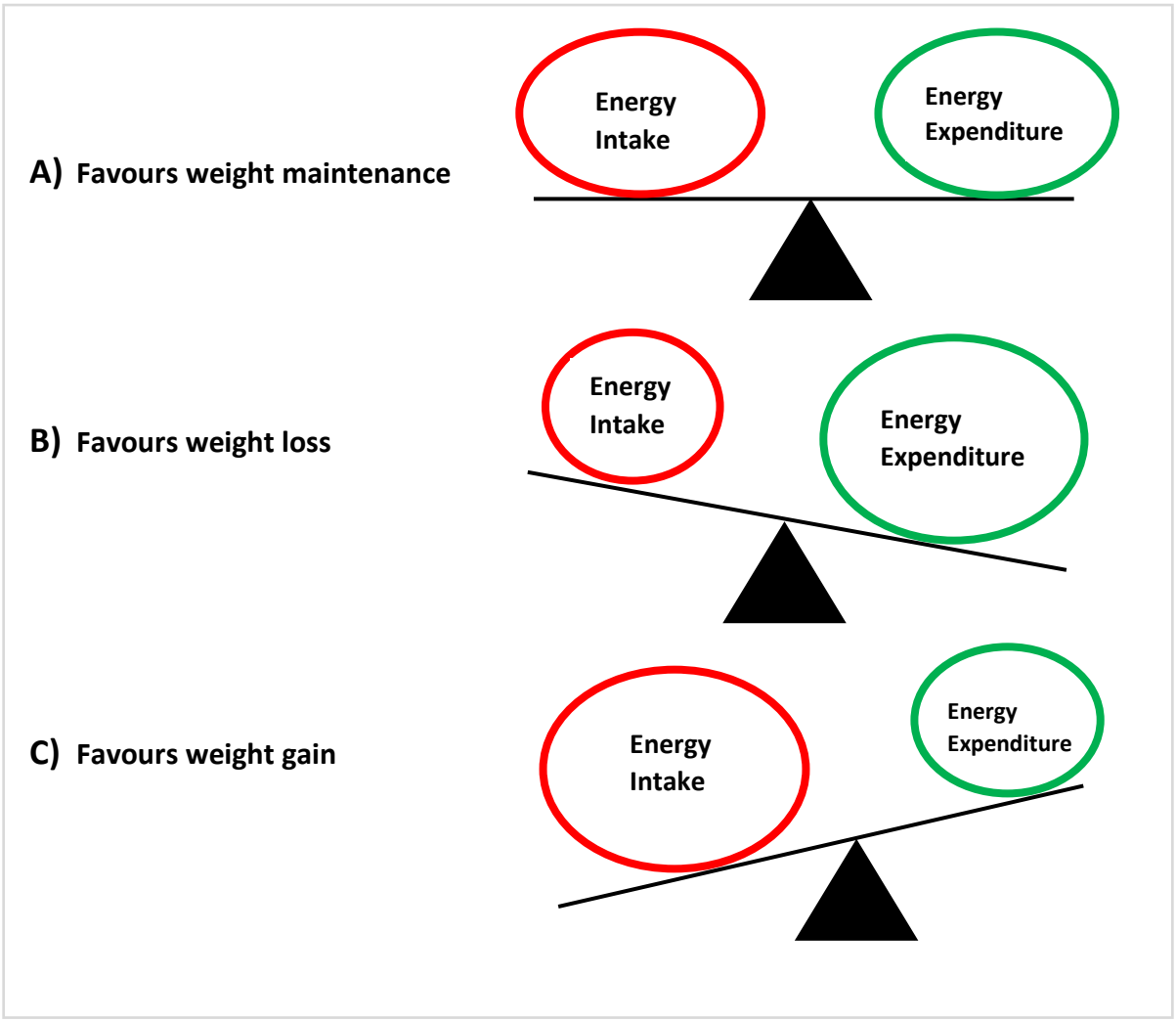


Figure 3. Three states of energy intake versus energy expenditure: A) Favours weight maintenance, in which energy intake equals to energy expenditure; B) Favours weight loss, in which energy expenditure is greater than energy intake; and C) Favours weight gain, in which energy intake is greater than energy expenditure.

WHO Classification	BMI (kg/m^2)
Underweight	<18.5
Normal weight	18.5 – 24.99
Overweight	25 – 29.99
Obesity Class I	30 – 34.99
Obesity Class II	35 – 39.99
Obesity Class III	≥ 40

Table 4. Classification of BMI (kg/m^2) based on the WHO criteria. Abbreviations: WHO; world health organisation, BMI; body mass index.

1.8.1.2. Obesity and other health conditions

Obesity plays a significant role in the onset, maintenance or aggravation of OSA as well as several other chronic health-related issues including cardiovascular disease, T2DM, hypertension, heart failure, and stroke (123-127). Obesity is also associated to comorbidities such as mental health issues (e.g., anxiety and depression), high levels of absenteeism (128) and increased risk of all-cause mortality (129).

1.8.1.3. The relationship between OSA and obesity

Recent research has hypothesised that a reciprocal relationship between OSA and obesity likely exists. That is to say, that being obese is known to play a role in causing OSA, and the presence of OSA may also be likely to increase an individual's propensity towards gaining weight.

Obesity causing OSA: On one hand, obesity can lead to OSA through its impact on several of the mechanisms known to cause OSA. Specifically obesity has been shown to (1) increase upper airway narrowing and therefore airway collapsibility, (2) reduce lung volumes which will also likely contribute to an increase in airway collapsibility via reductions in caudal traction, and (3) make breathing more unstable which has also been shown to be a trait involved in OSA pathogenesis (130) (Figure 4).

OSA causing obesity: On the other hand, the presence of OSA may potentially further increase obesity levels via a number of proposed mechanisms: a) Given that OSA causes fragmented sleep, poor sleep quality, and sleep deprivation (131), a reduction in physical activity levels and therefore energy expenditure may occur due to the associated sleepiness/fatigue. Furthermore, reduced or fragmented sleep has also been shown to result in an hormonal imbalance, metabolic dysregulation and systematic inflammation. Such conditions may lead to positive energy balance, obesity and metabolic syndrome (94, 132, 133); b) Sleep deprivation has also been suggested to contribute to weight gain in a group of healthy men. The increase in weight mainly occurred through imposing changes in an individual's dietary choices and eating behaviour. Such changes in eating behaviour were mainly based on emotional and psychological needs rather than any changes in individual's actual calorie requirements (134). It has been also revealed that in healthy individuals, the magnitude of alterations in the increased intake of high calorie foods is positively correlated with the perceived subjective severity of sleep deprivation (135). However, to date the majority of the evidence supporting this causal pathway comes from studies in healthy individuals. Therefore, the field is in need of similar studies in OSA patients before we can firmly conclude that OSA is indeed a contributing factor towards obesity.

Weight gain in obese individuals, either with or without OSA, is suggested to attribute to resistance of leptin (the satiety-inhibiting hormone produced by adipocytes) and

subsequently further weight gain (136, 137). Obesity and increased number of fat cells enhance leptin levels in the body which may develop body inflammation and leptin resistance. Leptin resistance may contribute to the generation of misleading signals that informs brain of the existence of low leptin concentration in the body. Such disrupted signals may lead brain to signal hunger which may result in continuous food cravings and overeating. Such mechanisms may lead to further obesity and contributes to a vicious cycle of increasing metabolic impairment (136, 137) (Figure 5).

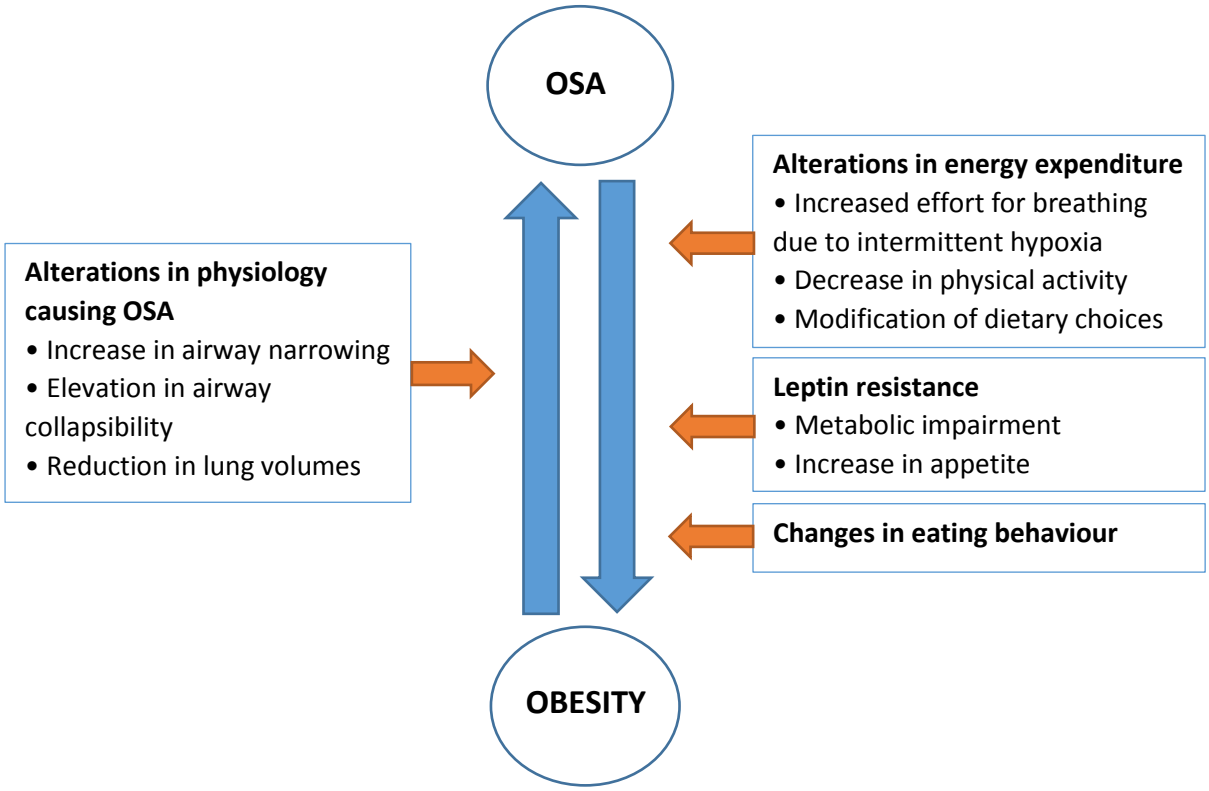


Figure 4. A display of potential mechanisms between OSA and obesity, which may format a vicious cycle.

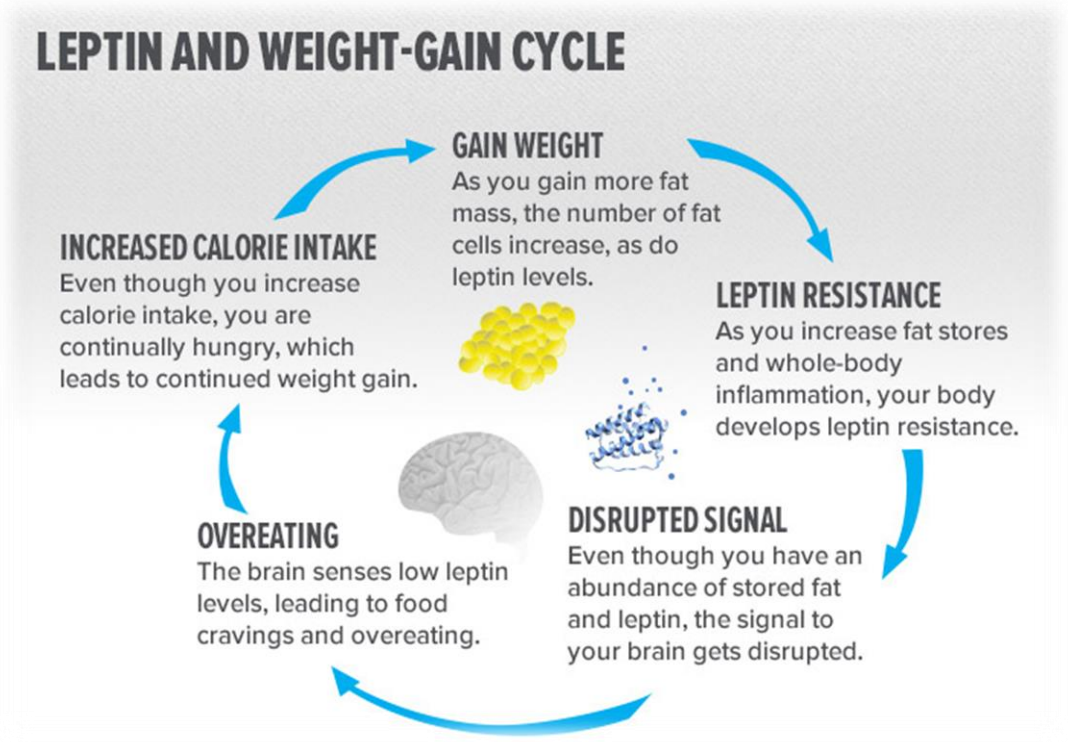


Figure 5. An illustration of the positive-feedback loop via which leptin/leptin resistance contribute towards obesity levels (138).

In healthy individuals, the highest secretion level of leptin initiates from midnight to early morning, which attributes to a suppressed appetite while sleeping during the night (139). However, conditions such as sleep fragmentation and sleep deprivation which are strongly associated with OSA may lead to a reduction in nocturnal leptin levels and elevation in appetite and food intake (140-142). This suggests that people are likely to want to eat more when have fragmented sleep or sleep deprivation. So far, many studies focused on exploring the effects of sleep fragmentation and sleep deprivation on the level of leptin secretion/resistance in OSA patients (143, 144). However, there is still no evidence of the potential influence of OSA-associated factors (e.g., elevated leptin levels) on the food intake/eating behaviour in patients with OSA.

1.8.1.4. Obesity, OSA and eating behaviour

Eating behaviour may affect body weight by influencing energy intake through choices about when and where to eat, as well as the types and amounts of foods chosen (145, 146). The state which determines each individual's susceptibility for following unhealthy eating behaviours is complex and varies based on the different internal and external factors such as individual characteristics (taste preferences, self-discipline, convenience, and time), physical environment (food availability and accessibility, appeal and food products affordability), social network influences (friends and peers), and macro environment (media and advertising)

(147). In addition to these factors, anything that reduces the amount of sleep obtained, including sleep disorders such as OSA, may substantially affect energy intake through imposing hormonal changes that exacerbate hunger and alter one's eating behaviour as described above. Such behaviour can therefore subsequently lead to weight gain, enhanced glucose levels, insulin resistance, and increased risk of diabetes and metabolic syndrome (94, 132, 148-152)

It has been suggested that a 10% weight gain is associated with a six-fold increased risk of developing OSA, whereas a 10% decrease in weight is associated with 26% reduction in AHI level (59). Thus, investigating one's eating behaviour may pinpoint the pathways leading to obesity. Such findings result in identifying required alterations in food-related behaviours which may inhibit the development of obesity and its associated comorbidities such as OSA.

1.8.1.5. How to assess eating behaviour?

Different tools are currently available for assessing adults' eating behaviour which include Dutch eating behaviour questionnaire (DEBQ), three factor eating questionnaire (TFEQ), and TFEQ-R18 (a shortened version of TFEQ including 18 questions). Among these tools, the TFEQ-R18 is by far one of the most commonly utilised questionnaires for assessing eating behaviour and has been employed in a variety of different populations (153-157). The shortened version of the eating behaviour questionnaire (TFEQ-R18) is suggested to be well suited for use in epidemiological studies or clinical trials, since it reduces the burden placed on the participants whom often are asked to complete multiple questionnaires (158).

In order to assess eating behaviour, the TFEQ-R18 measures three aspects comprising cognitive restraint, uncontrolled eating, and emotional eating which are defined below.

1. Cognitive restraint assesses whether an individual consciously restricts food intake in order to control body weight (153, 159).
2. Uncontrolled eating assesses an individual's control over their food intake (153, 159).
3. Emotional eating refers to eating in order to satisfy emotional needs, where there is a tendency to overeat in response to emotional states such as anxiety or depression (153, 159).

Some previous studies have reported significant relationships between the three aspects of eating behaviour and key factors including BMI, total energy intake, and a certain type of food intake (153, 154). Such findings are reported in detail below.

In a sample of young females (aged 17-20 years), a significant association was found between higher BMI and increased levels of cognitive restraint and emotional eating, but not with uncontrolled eating (153, 154). However, another study found a significant association between higher scores of cognitive restraint and lower energy intake among 14-27 year old

girls (154). In the general population (529 middle-aged adults and 358 teenagers), higher energy intake was associated with greater levels of uncontrolled eating in adult men than women (154). Cognitive restraint in adults was positively associated with higher intake of a certain type of food (e.g., green vegetables), while it was negatively associated with consuming other type of food (e.g., sweet and fatty products) (154). An elevated intake of snacks was seen in adult emotional eaters, whereas those with high scores of uncontrolled eating showed a greater intake of energy-dense foods (high in fat content) (154).

Eating behaviour and food preferences have repeatedly showed to be significant predictors of higher BMI and obesity in adult population (160-162). However, it is unclear whether losing weight can predict changes in eating behaviour. Understanding individuals' eating behaviour is important for obtaining a clearer picture of the pathways leading to weight gain and obesity. By far, there are limited studies assessing eating behaviour in different populations. *More importantly, no study to date has assessed eating behaviour in OSA patients.* Conducting such studies may provide a better understanding of the underlying factors attributing to weight gain in OSA patients who are already at a higher risk of obesity compared to healthy individuals.

1.8.2. Depression and anxiety

1.8.2.1. Depression and its diagnosis

Depression is a chronic condition in which a person experiences a substantial change in his/her mood and feelings about the world and himself/herself. Depending on the severity of depression, people may have different physical or psychological symptoms. Depression may lead individuals to a lack of connection with their surrounding world and consequently pushing them into social isolation (163). Depressed people may experience persistent feelings of sadness, helplessness and hopelessness. Such frequently disrupting feelings may result in inabilities in concentration and performance in normal daily activities (164). Depression is often associated with altered patterns of circadian rhythms and sleep disturbances (165). Many potential long-term complications may occur in a severe depression, which may eventually lead depressed patients to believe that suicide is the only way for dealing with their seemingly insolvable problems (163, 166).

According to the Diagnostic and Statistical Manual of Mental Health, Fourth Edition (DSM-IV) (167), clinical depression is a common mood disorder characterised by the presence of one or more major depressive episodes with no history of manic, mixed, or hypomanic episodes. The existence of five of the nine following DSM-IV symptoms for a minimum period of two weeks is required for an appropriate diagnosis of depression: (a) feeling depressed; (b) loss of interest or pleasure in daily activities/outside stimuli; (c) significant changes in weight or appetite; (d) insomnia or hyposomnia; (e) psychomotor retardation or agitation; (f) loss of

energy and fatigue; (g) feelings of worthlessness or guilt; (h) diminished ability to think or concentrate; and (i) suicidal ideas.

1.8.2.2. Anxiety and its diagnosis

Anxiety is the most prevalent mental health disorder in which a person experiences consistent feelings of apprehension and dread not as a response to an immediate threat, but as an emotional reaction to the continuous expectation of future threat (168). Such persistent attempts to cope while approaching a potential danger/threat, leave a person in an unpleasant feelings of fearfulness which does not seem to have an endpoint. Anxiety disorder may lead to decreased social interaction and reduced productivity, as well as increased rates of morbidity and mortality (169, 170). Anxiety disorders are often accompanied by other chronic disorders such as depression and eating disorders (171, 172).

According to the Diagnostic and Statistical Manual of Mental Health, Fourth Edition (DSM-IV) (167), anxiety disorder is a clinical condition characterised by the presence of three or more of the following six symptoms occurring more days than not, for at least 6 months: (1) restlessness, (2) being easily fatigued, (3) difficulty in concentrating or mind going blank, (4) irritability, (5) muscle tension, and (6) sleep disturbance (experiencing difficulties in sleep onset or staying asleep, or having a restless unsatisfying sleep).

1.8.2.3. The coexistence of depression and anxiety

The co-occurrence of depression and anxiety disorders is extremely common (173, 174). Nearly, 50% of the patients in a primary care setting have showed to suffer from a comorbid second depressive or anxiety disorder (174). A longitudinal study of 19 and 20 year old community residents in Switzerland (175) suggested a rare transition from depression to anxiety during a 15-year period, in which only a 9% (range, 0.04-0.13) of those with depression alone experienced anxiety alone. In contrary, nearly half of those with anxiety alone developed depression either alone or comorbid with anxiety at follow-up. A transition to comorbid anxiety and depression occurred in 21% (range, 0.14-0.22) of those with depression alone and 24% (range, 0.17-0.32) of those with anxiety alone (175). Interestingly, a longitudinal evidence showed that anxiety usually develops into depression almost as often as depression develops into anxiety (176). An average 12% of the participants reported comorbid depression and anxiety, of whom 66% and 47% had recurrent depression and anxiety, respectively. Comorbid anxiety and depression is found to be associated with more persistent and severe symptoms than either disorder alone (175, 177). Even though depression and anxiety may coexist in many cases, but (1) there is not a consistent pattern of transition from anxiety to depression or vice versa, and (2) depression and anxiety disorders are two independent clinical conditions and need to be assessed and treated as such (176, 178).

1.8.2.4. Assessment of depression and anxiety

So far, it is unknown if depression and anxiety can be measured with a specific biological marker. Thus, there is a lack of laboratory test to detect/distinguish between depression and anxiety. The diagnosis of depression and anxiety must be done by a health care professional, through employing a series of reliable scales and objective measures (179), including but not limited to the Hospital Anxiety and Depression Scale (HADS), the Beck Anxiety Inventory (BAI), and the Beck Depression Inventory-second version (BDI-II).

Hospital Anxiety and Depression Scale (HADS)

The Hospital Anxiety and Depression Score (HADS) (Appendix 6) was initially developed in 1983, as a 14-item ordinal scale to determine the levels of anxiety and depression in people with physical health problems. However, validity of the HADS is not limited to patients in hospital settings. A review of the 747 studies suggested that the HADS questionnaire was a valid way of assessing the symptom severity of anxiety disorders and depression in the general population and also in primary care medical practice (180). However, the HADS questionnaire is not a diagnostic tool and definite diagnosis must be confirmed through clinical examination (181, 182).
The HADS questionnaire evaluates participants feelings during the past week by collecting answers to seven items related to anxiety with the remaining seven items related to depression levels (183). The HADS questionnaire is mostly used to detect levels of anxiety and depression in those with physical ill-health. The HADS questionnaire focuses more on non-physical symptoms without considering factors such as appetite, sleep and self-harm/suicidal thoughts (184). Each subscale (depression or anxiety) scores can be used to categorise symptoms of anxiety or depression into three levels of severity (see Table 5).

Beck Depression Inventory – second version (BDI-II)

The Beck Depression Inventory (BDI) is one of the most widely used assessment tools in measuring intensity of depression experienced in psychiatric and normal population (96). A second version of BDI, referred to as the BDI-II is also a common tool in assessing depression symptoms in different types of population (Appendix 7). The BDI-II evaluates psychological and somatic manifestations of depressive episodes in a period of two-weeks, as operationalised in the DSM-IV (167).

Results from a review of 118 studies reported that the BDI-II is a simple, short, and reliable tool, with a high capacity for detecting depression in various settings (185). The BDI-II comprises 21 self-rated questions, assessing feelings of hopelessness and irritability, guilt or feelings of being punished and physical symptoms such as fatigue, changes in appetite, and lack of interest in sex, experienced during a past two-weeks (96). The BDI-II can be used to categorise depression in four levels of severity (see Table 5). To assess the individual's mental

state, the BDI-II can be used in conjunction with other tests, but it cannot be utilised solely as a diagnostic tool for clinical depression (96, 111).

Classification of severity level	BDI-II scores for depression	HADS scores for anxiety and depression
Normal	0-9	0-7
Mild	10-18	8-10
Moderate	19-29	11-14
Severe	30-63	15-21

Table 5. Classification of anxiety and depression severity level based on the scores generated from the BDI-II (only used as a depression measurement tool), and HADS (used as a depression and anxiety measurement tool) questionnaires. Abbreviations: BDI-II; Beck Depression Inventory-second version, HADS; Hospital Anxiety and Depression Scale.

1.8.2.5. OSA and depression/anxiety

Depression and anxiety are the most commonly reported psychological symptoms in patients with OSA (186) with rates being higher compared to the general population (97, 187). The proportion of the global population with depression and anxiety disorders is estimated to be 4.4% and 3.6% respectively (188). Although there is not such a global record of the prevalence of anxiety and depression in the population with OSA, however it has been suggested that 53% and 46% of the population with OSA suffer from anxiety and depression symptoms, respectively (97). A review of 55 studies revealed a prevalence of 7-63% for depression and 11-70% for anxiety in a population of men diagnosed with OSA (96). Importantly, previous studies suggested that the prevalence of anxiety and depression symptoms in a population with OSA is higher among women than men (189-192). Asghari et al. (192) reported that anxiety symptoms were present in 73.6% of women versus 53.4% of men. However, depressive symptoms were shown in 70% of women versus 49% of men (192). Elevated rates of depression and anxiety in OSA population have been repeatedly reported to be associated with the existence of OSA and its increasing severity (96, 97, 193, 194).

Scores of psychological well-being (with considering conditions such as depression and anxiety) were significantly lower in OSA patients compared to healthy matched controls (193). Such reduced psychological well-being in OSA patients was reported to be positively related to excessive daytime sleepiness and sleep fragmentation (193, 195-197), both of which are widely known for their association with anxiety and depression (198-200). A longitudinal study (18-year follow-up) suggested the existence of a potential causal link between OSA

severity and depression, where moderate to severe OSA patients presented a 2.6 times greater odds of developing depression after adjusting for potential cofounders (201). However, this finding has not always been consistent as other investigations have demonstrated that depressive symptoms were directly correlated with the severity of OSA in one (194), but not another study (192). These discrepant findings may be explained by various reasons that include the differences in the study design, selection characteristics and heterogeneity of the study populations. Hence, so far, there is not enough evidence to firmly confirm whether there is a relationship between depression levels and OSA severity.

Obesity, which is commonly seen in OSA patients, has also been positively correlated with the risk of developing depression and anxiety (122, 202, 203). Furthermore, depression and anxiety are also suggested to contribute to weight gain and obesity (204-206). Unhealthy eating behaviours have also been associated with depression (207), while by contrast, an intake of healthy diet (e.g., Mediterranean diet) has been shown to be associated with reduced levels of anxiety and depression (208). Interestingly, depressed individuals have been more likely to consume certain type of foods including processed, fried and sugary products (209). A systematic review of longitudinal studies indicated that the presence of depression at baseline enhances the risk of becoming obese at follow-up by 58% (OR, 1.58; 95% CI, 1.33-1.87; $P < .001$), while the existence of obesity at baseline similarly increases the risk for occurrence of depression at follow-up by 55% (unadjusted OR, 1.27; 95% CI, 1.07-1.51; $P < .01$) (210). Thus, OSA patients seem to be at high risk of gaining weight and developing a mental health disorder. In summary, the existence of either depression or obesity in OSA patients may predispose or exacerbate the occurrence of the other condition.

1.8.2.6. Comorbid OSA and depression/anxiety – implications for treatment

OSA and depression/anxiety may easily mimic symptoms of one another and make under-diagnosis of the other condition more possible (186, 187). Many individuals with OSA symptoms, are diagnosed as having anxiety and/or depression before they are referred for assessment of their sleep disorder (211). Thus, it is common that individuals with OSA are referred for an assessment of their sleep when they are already receiving antidepressant medications (212). Sleep problems are not frequently assessed in patients with anxiety or depression, which may be a reason for antidepressant treatment failure in this group of population (187). The overlap between anxiety/depressive symptoms and OSA along with the high prevalence of both depression and OSA in communities may result in the diagnosis and treatment of anxiety and depression rather than OSA in many individuals (187, 194). In particular, a presence of similar symptoms such as disturbed sleep, fatigue, and irritability for both depression and OSA may contribute to the potential for diagnostic confusion between the entities (213, 214).

For individuals with overlapping symptoms of OSA and anxiety/depression, a careful assessment of OSA and depressive symptoms seems to be necessary, while OSA is

recommended to be treated first (see description of OSA treatment below) and is recommended to occur before starting other treatments for anxiety/depression symptoms (187, 215). Further, the comprehensive assessment of comorbidities which may interact which each other in patients with OSA (anxiety/depression and obesity) allows health practitioners to provide a more accurate diagnosis, implement appropriate strategies in goal setting during treatment and follow-up visits (216).

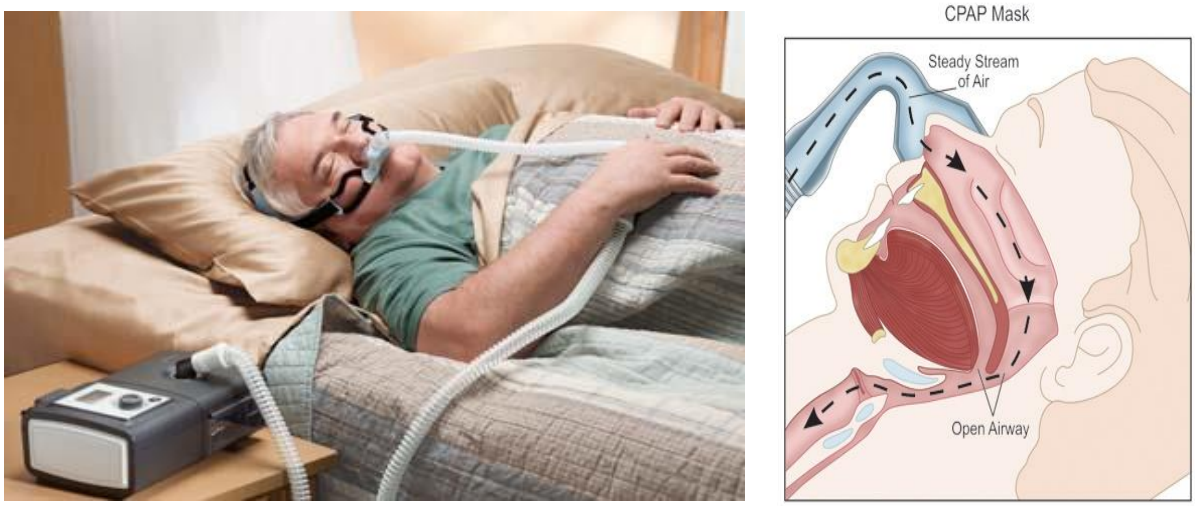
The common treatments for depression and anxiety disorders are psychopharmacological and cognitive–behavioural interventions (217). However, effective treatment methods for patients must be chosen based on the definite diagnosis of the condition(s) which should be confirmed before initiating a treatment which may solely target OSA or anxiety/depression (187). Diagnosis and treatment of anxiety and depression as well as obesity as common conditions associated with OSA in conjunction with an effective therapy for OSA is recommended (187). Such comprehensive treatment of accompanied conditions may potentially result in weight loss and reduction of anxiety/depressive symptoms at the same time as it increases the effects of OSA treatment.

1.9. Treatment of OSA

The most appropriate treatment for OSA varies according to the severity of the individuals OSA and a variety of other factors which include, but are not limited to age, body-weight, degree of daytime sleepiness, medical history, and anatomy of the upper airway (218). As such treatment is often individualised by a specialist based on the each patient's preferences and symptomology (219).
There are a number of treatment options for patients with OSA, but the most commonly recommended therapies are continuous positive airway pressure (CPAP), oral appliance, sleep hygiene improvement, and weight loss programs (218, 219). An ideal therapy for OSA patients should be chosen based on its effectiveness, affordability and accessibility (67, 220).

1.9.1. CPAP therapy

Currently, CPAP is the first-line therapy for clinically-significant moderate to severe OSA, and is considered the "gold standard" treatment (221, 222). CPAP is a device utilised to prevent the airway from repeatedly collapsing by providing a positive pressure inside the airway during sleep (35). Such positive pressure is achieved by the pumping of air at a pressure via a mask covering the nose or nose and mouth which acts as a pneumatic splint to keep the airway open (Figure 6). The appropriate mask should be chosen based on the facial anatomy of the patient, in order to provide optimal seal and maximum comfortability.



[Image source from: UKCPAP. CPAP therapy for OSA 2011 [Available from: https://www.ukcpap.co.uk/cpap.php.]

Figure 6. An example of an OSA patient using continuous positive airway pressure (CPAP) during sleep. CPAP machines deliver a continuous pressure and that acts to splint open the airway and prevent airway collapse.

A number of studies have examined the relationship between average nightly CPAP use and its impact on several of the negative consequences of OSA (223-225). A common finding amongst these studies shows that a dose-dependent relationship exists, meaning that the more hours of using a CPAP offers the greater benefits. More specifically, OSA patients with over seven hours of daily CPAP adherence experience the most clinical benefits including normal neurocognitive function (223, 226). Furthermore, a high compliance to CPAP therapy improves many of the other negative consequences of OSA (227, 228).
Even though a high compliance to CPAP therapy improves many of the negative consequences of OSA (227, 228), it may also be accompanied with unwanted side effects which may reduce patients' adherence to CPAP treatment (229, 230). Side effects which may potentially decrease compliance with CPAP therapy include nasal dryness and congestion, claustrophobia, facial skin abrasions, air leaks, and conjunctivitis (230, 231).

Importantly, anxiety and depression have been showed as two major risk factors for long-term adherence to CPAP therapy (232, 233). Therefore, anxious and depressed individuals are less likely to comply with CPAP treatment. From the opposed point of view, successful treatment of OSA with CPAP therapy has repeatedly showed to result in alleviation of depression (194, 234-237) and anxiety symptoms (97, 234, 236). Putting together, the evidence suggest (a) a necessity for considering anxiety/depression symptoms when introducing one to CPAP therapy, and (b) a need for greater level of support and potential adjunctive therapy for anxiety/depression when initiating CPAP therapy for a patient with anxiety and depression symptoms.

1.9.1.1. CPAP therapy and weight gain

While CPAP therapy relieves many of the symptoms and consequences attributed to OSA, there is emerging evidence that using CPAP may actually cause individuals to gain weight, which would in turn be expected to worsen OSA symptoms (238, 239). However, it is worth noting that the relationship between CPAP therapy and weight gain has not always been reported (240, 241).

In contrast to healthy individuals, OSA patients, especially those with greater disease severity display a higher energy expenditure when sleeping (due to recurrent respiratory events during sleep) (242). Once CPAP therapy is initiated, energy expenditure is suggested to decrease during sleep, as a result of an undisturbed and better quality sleep (242). This evidence suggests that if this study cohort, especially those with higher OSA severity initiate CPAP therapy without increasing their energy expenditure, they are biased towards gaining weight by initiating CPAP therapy. A recent meta-analysis of 25 randomised controlled trials (RCTs) highlighted that overweight and obese participants who had been treated with CPAP experienced a weight gain (Hedges' g=0.17, 95% CI 0.10 to 0.24, I2 =0%, p=0.647) compared to control conditions. The delta weight (weight post-intervention minus pre-intervention) in CPAP users versus non-CPAP users were 0.417±0.718 kg and -0.096±0.718 kg, respectively (243). This synthesis of the available evidence identified the baseline weight of the participants as the sole predictor of an increased BMI after CPAP treatment for periods between 1 month to 4 years (243). The weight gain reported in untreated OSA patients highlighted the hypothesis stating that untreated OSA may cause obesity. However, there is no previous evidence to illustrate whether a) the weight gain in CPAP users and non-CPAP users, resulted due to the storage of the same type of tissue (e.g., fat, lean), or b) the storage of different type of tissues has affected these two groups differently. Other evidence suggested that an increased BMI observed in OSA patients initiating CPAP therapy may be partly explained by a reduction in leptin levels which may play a role in increasing appetite, and altering food intake (244-246).

Perhaps more importantly, the impact that CPAP has on a patient's BMI also seems to show a dose-dependent relationship. Specifically, a randomised controlled trial which introduced CPAP therapy over a period of 6 months, revealed that CPAP users may gain a modest amount of weight (0.35 ± 5.01 kg) (238). However, patients who were highly compliant with CPAP therapy tended to experience a greater increase in their BMI levels compared to non-adherent CPAP users (1.0 ± 5.3 versus -0.3 ± 5.0 kg, *P*=0.014) (238). A further retrospective case-control study showed that a 1-year of CPAP therapy leads to an increase in BMI of some, not all participants. Interestingly, no significant change in BMI has been observed in men after a 1-year of CPAP therapy. However, both women and also non-obese participants experienced an increase in BMI after a 1-year of CPAP therapy (23). By contrast, two non-randomised studies by Loube et al. (247) and Chin et al. (248) suggested that weight loss may have been facilitated in overweight and obese patients with OSA by the use of CPAP. Loube

et al. (247) reported that CPAP-compliance of more than 4 hours per night for a period of 9 months may have attributed to the weight loss of greater that 4.5 kg in participants with overweight and obesity. Similarly, Chin et al. (248) suggested a decrease in BMI of ≥ 1 kg/m^2 and ≤ 1 kg/m^2, respectively in 9 and 13 participants with severe OSA who underwent 6 months of CPAP therapy. However, weight loss may have accidently occurred in these two studies (247, 248) due to factors such as a) lack of well-matched controls which may have made the results of the study less reliable (248), b) decreased daytime sleepiness which may have possibly attributed to increased physical activity and enhanced energy expenditure, and c) metabolic changes beneficial to weight loss which may have happened in CPAP users independent of the levels of physical activity (247, 248). Thus, individuals who are undergoing CPAP therapy without imposing changes in their lifestyle (increase in energy expenditure or decrease in energy intake) seem to be more prone to weight gain and obesity (23).

1.9.2. Weight loss programs

Several OSA treatments including CPAP therapy and oral appliances can effectively relieve many of the symptoms experienced by individuals with OSA. However, regardless of the level of OSA severity, introducing conservative approaches such as weight loss programs have been strongly encouraged to help reduce symptoms in OSA patients (31). Successful weight reduction can provide a wealth of health benefits for not only the management of OSA and mitigating its symptoms (243, 249), but for reducing obesity levels and obesity-related comorbidities such as cardiovascular disease and metabolic syndrome. However, many barriers exist in promoting weight loss and preventing further weight gain once weight loss is achieved (250). OSA patients are considered a vulnerable population to weight gain and CPAP treatment, if prescribed, has been shown to either be associated with small decreases (247) or increases in weight (23) depending on the study. Thus, it is important to understand the impact of commencing a lifestyle intervention at the most effective time point during CPAP treatment to help this population to manage their weight.

Many lifestyle interventions have been conducted, applying different types of diet and exercise (either in isolation or in combination) in OSA patients. Two recent reviews by Araghi et al. (251) and Mitchell et al. (252) have investigated the effectiveness of the lifestyle interventions. A systematic review and meta-analysis by Araghi et al. (251) has included 21 studies, comprising 7 RCTs and 14 non-RCTs, revealing that weight loss in OSA patients may reduce AHI levels and frequency of the drop in blood's oxygen level per hour of sleep referred as oxygen desaturation index by 4% (ODI4) (251). Further evidence including ten studies, comprising RCTs and systematic reviews, which was provided one year later by Mitchell et al. (252) supported findings of the study by Araghi et al. (251).

Importantly, by far, there have not been any systematic reviews specifically of randomised controlled trials assessing which lifestyle intervention (diet, exercise or a combination of the two) delivers the greatest benefit in reducing OSA severity. Conducting such study would fill

a gap in the literature by providing information on the effectiveness of diet and exercise, either in isolation or combination on reducing OSA severity.

1.10. Aim of the thesis

The overall aim of this thesis is to fill a number of the current gaps in our knowledge by identifying effective treatments for OSA as well as a better understanding of the relationship between OSA severity, BMI, eating behaviour, anxiety and depression symptoms in patients with OSA.

The first study (chapter 2) aims to identify whether a diet or exercise intervention, either alone or in combination, is more effective at reducing OSA severity. In order to achieve this aim, a systematic review and meta-analysis of the RCTs was conducted to reveal the effects of OSA treatment and its consequences.

The second study (chapter 3) aims to explore the association between OSA severity, BMI levels, three aspects of eating behaviour (cognitive eating, uncontrolled eating, and emotional eating), and symptoms of anxiety and depression in newly diagnosed adults with OSA who are overweight/obese. Thus, chapter three intends to further the knowledge of the factors associated with OSA severity at the time of diagnosis and better understand what additional support these patients may require in their treatment journey.

Chapter 2: Assessing the effects of diet, exercise and the combination of the two as a treatment for OSA: a systematic review and meta-analysis

2.1. Introduction

Obstructive sleep apnoea (OSA) is a common sleep disorder characterised by repeated collapse of the upper airway during sleep exposing the sufferer to intermittent hypoxia, frequent arousals, and sleep fragmentation (253). Importantly, OSA is associated with a wide range of adverse health consequences, including cardiovascular disease, metabolic disorders, and cognitive impairment (254, 255).

Continuous positive airway pressure (CPAP) has been adopted as the most common treatment for moderate-severe OSA, and is considered the "gold standard" therapy (254, 256). However, recent evidence has suggested that the compliant use of CPAP might be associated with a small yet significant weight gain over time (257). Given that obesity is the largest independent risk factor for developing OSA and other co-morbidities (130, 252) and that CPAP therapy may actually cause people to gain weight over time, lifestyle interventions which aim for weight loss are clinically recommended as an additive therapy in the management of OSA and its associated co-morbidities.

Many randomised controlled trials and systematic reviews including our own meta-analysis (252) have assessed the impact that lifestyle interventions such as diet and exercise have had on losing weight and reducing OSA severity (251, 258, 259). The findings from these studies confirm that diet and exercise typically decrease OSA severity. Interestingly, evidence from a few studies gathered in a meta-analysis by Iftikhar et al. suggested that exercise alone, even with minimal changes in body weight reduces OSA severity (260). However, to date there have been no systematic reviews specifically of randomised controlled trials to examine which lifestyle intervention (diet, exercise or a combination of the two) delivers the greatest benefit in reducing OSA severity. Therefore, we aimed to conduct a systematic review and meta-analysis of randomised controlled trials investigating the effectiveness of diet and exercise, either in isolation or combination on a) OSA severity and b) change in BMI.

2.2. Material and methods

2.2.1. Data sources

We included studies where the target population was defined as adults aged over 18 years, diagnosed with OSA (defined by an AHI>5 events/hr), and the intervention was specified as any lifestyle intervention including diet, physical activity, and behaviour-modifying programs.

Our primary outcome measure was the severity of OSA as measured by the apnoea-hypopnoea index (AHI). The secondary outcome measure was weight measured by the body mass index (BMI). All randomised clinical trials that met the inclusion criteria were eligible for review (1980-June 2016). Other study designs including cohort studies, case studies, literature reviews, meta-analysis, narrative reviews, as well as commentaries, letters, conference abstracts and protocols were excluded and cross-reviewed for exclusion by two of the reviewers (one of which was myself). Studies which enrolled patients with chronic heart failure, presented weight-loss as a result of bariatric surgery, and those that included a physiotherapy-based exercise intervention and no vigorous physical activity intervention were also excluded.

2.2.2. Study selection

This systematic review was conducted in July 2016 through searching five databases including CINAHL, Cochrane, Embase, OVID Medline, and Scopus. A combination of following keywords were used:

sleep, diet*, food*, eating*, beverage*, nutrition*, exercis*, physical* activ*, fitness*, and sport**

These keywords were used in a slightly different way for each database (Appendix 1). For the Scopus database, search queries included “sleep apnea” and “obstructive sleep apnea”. In searching CINAHL, Cochrane, and OVID Medline, “sleep apnoea, obstructive” was incorporated as a MeSH heading. For Embase, the terms “sleep apnoea” and “sleep apnea” were used. Searches in CINAHL, Embase, and OVID Medline were limited to human studies published in English. We did not limit the language of published works in the Cochrane and Scopus databases because there was no option for limiting the target population and language. All queries were limited to publications since 1980.

2.2.3. Eligibility criteria

Database search results were screened for duplicates using EndNote (Version 7.0.2, Thomson Reuters, 2013). Once duplicates were removed, titles and abstracts of studies were screened for eligibility to include, using a star-rating system to code publications for inclusion. All studies that comprised the relevant populations, interventions, and outcomes were included.

The full-text of the included papers were then reviewed to exclude further papers that did not meet the review inclusion criteria. To further identify relevant studies, articles’ reference lists from already-included studies were cross-compared. Subsequently, reference lists of the retrieved articles were examined, and as a result one additional relevant study was included (261).

2.2.4. Data extraction and assessment of risk of bias

Data was extracted according to National Health and Medical Research Council (NHMRC) Data Extraction form for randomised controlled trials and cohort studies (262). Data extraction of each eligible study was performed independently by two reviewers (one of which was myself), and then the extracted data was cross-checked by a third reviewer and any disagreements were discussed and resolved. Two independent reviewers (one of which was myself) reviewed the risk of bias of individual studies using Cochrane's risk of bias tool (263). The presence of potential publication bias in this area of investigation was assessed using funnel plots (see Figure 7 and 8).

2.2.5. Synthesis of results and statistical analysis

Two meta-analyses were conducted to examine the effect of lifestyle interventions, including diet and/or physical activity or other lifestyle-modifying programs. One was conducted using AHI as the outcome measure, the other using BMI as the outcome measure.

Inclusion in the meta-analysis was based on whether authors reported mean changes and standard deviation/error of AHI, and BMI following the study period for both intervention and control groups. The authors of 10 studies were contacted via email to provide this information. Complete data was provided for 8 studies which were included in the meta-analyses (259, 264-270). Two of the contacted authors only provided information on AHI (265) or BMI (264), so these data were included in each respective meta-analysis only. Studies that did not provide correct information for inclusion in the meta-analyses were summarised narratively.

Random effects meta-analyses were undertaken to compare which intervention type had the largest effect on AHI and BMI reduction. To do this, Review Manager (RevMan) Version 5.3.5 (The Cochrane Collaboration, 2014) (271) was used. Meta-analyses were conducted using pre- and post-intervention mean change AHI and BMI along with their standard deviation from the studies, while stratifying studies into three subgroups based on the type of intervention applied (diet, exercise, or combination of the two). Statistical heterogeneity was assessed using the Cochran's Q and I^2 statistics. Meta-regression analyses were carried out using STATA (Version 14, StataCorp, 2015) (272) using a random-effects model and mean difference. Difference in mean changes in AHI and BMI between intervention and control group along with the corresponding standard error were used in performing meta-regression. Meta-regression analyses were used to identify whether the study characteristics of length of intervention and baseline AHI and BMI values explained variation in each meta-analysis dependent variable. We also examined whether between-study differences in changes in BMI explained variation in between-study variation in AHI.

2.3. Results

2.3.1. Studies included in meta-analyses

The summary of the search results can be found in Figure 7. A total of 7,420 publications were identified by the initial search of which, 19 of which were suitable to include in the systematic review. The pre- and post-intervention values from all 19 eligible studies are presented in Table 6. All studies were assessed using the Cochrane risk of bias tool (263) which is outlined in Figure 8. Out of the 19 studies, 12 RCTs were identified as eligible to include in the meta-analyses. Details of the RCTs included in meta-analyses and their follow-up studies (where applicable) are outlined in Table 7.

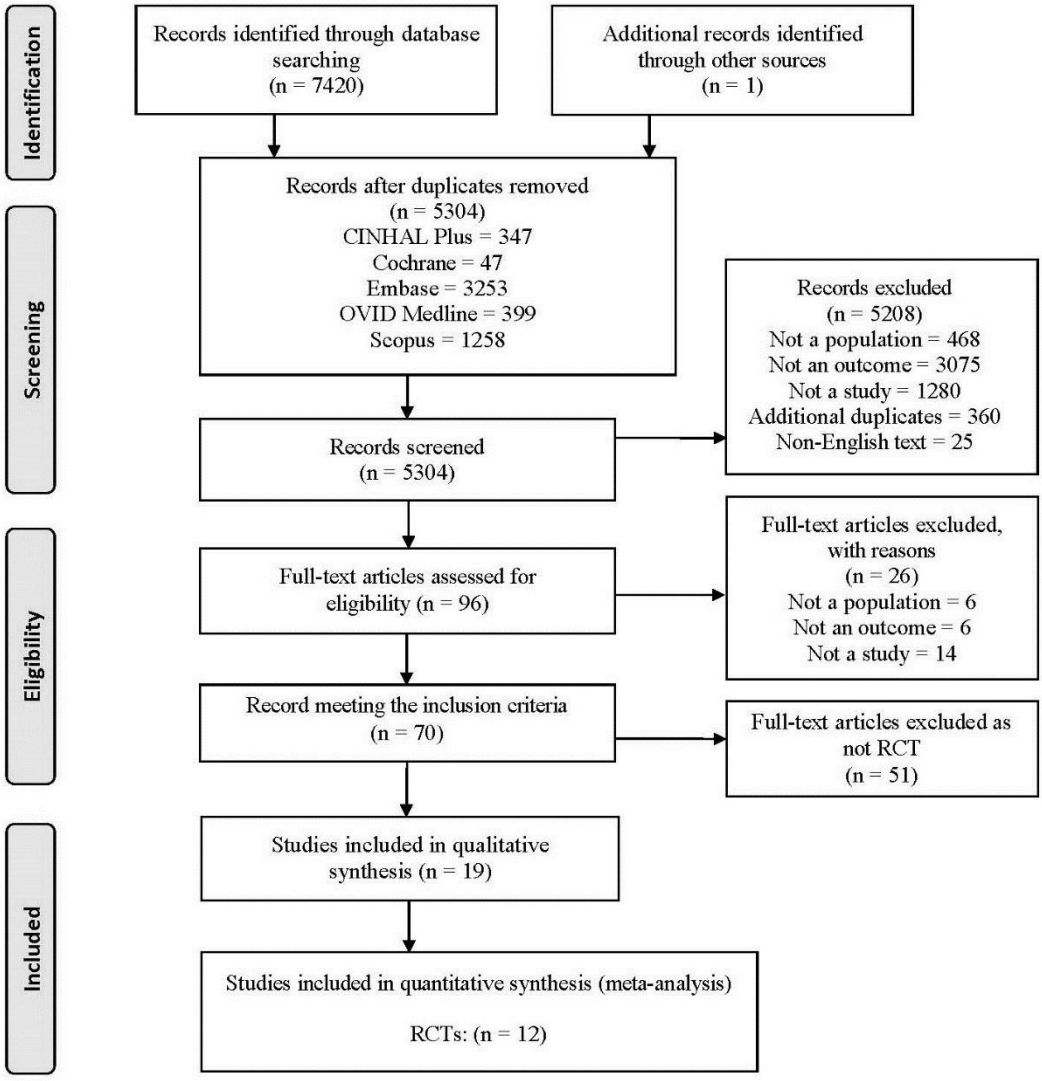


Figure 7. Identifying studies for inclusion. RCT, randomised controlled trial.

Table 6. Records of pre- and post-intervention Mean(SD) in age, body weight and OSA markers in 19 eligible studies in the systematic review.

Study (RCT or Follow-up)	Sample size and sex	Drop-out rate (%)	Group	Age in years	Weight at baseline (kg)	Weight after intervention (kg)	BMI at baseline (kg/m^2)	BMI after intervention (kg/m^2)	AHI at baseline (events/h)	AHI after intervention (events/h)	ODI_4 at baseline (episodes/h)	ODI_4 after intervention (episodes/h)
Ackel-D'Elia 2012 [265]	47 M	32	a	48.4 (9.2)	81.0 (10.0)	–	28.0 (3.1)	–	40.5 (22.9)	–	–	–
			b	49.5 (7.7)	84.4 (9.7)	–	28.5 (2.2)	–	42.3 (21.6)	–	–	–
Desplan 2014 [267]	26 M/F	11	a	–	85.0 (17.2)	82.6 (16.4)	29.9 (3.4)	29.1 (3.1)	40.6 (19.4)	28.0 (19.3)	23.1 (15.8)	17.6 (13.2)
			b	–	89.1 (11.6)	89.1 (10.8)	31.3 (2.5)	31.3 (2.2)	39.8 (19.2)	45.4 (22.5)	24.9 (12.4)	30.1 (23.1)
Fernandes 2015 [258]	29 M/F	28	a	39.09 (10.8)	100.08 (13.5)	94.51 (11.9)	34.60 (2.7)	32.73 (2.8)	26.67 (64.4)	19.45 (26.6)	19.36 (29.1)	12.96 (22.4)
			b	44.10 (6.2)	99.73 (14.2)	100.16 (16.3)	35.92 (2.9)	36.03 (3.4)	16.88 (8.6)	17.01 (11.0)	9.09 (5.3)	9.23 (6.3)
Foster 2009[1] [24]	264 M/F	17	a	61.2 (6.6)	102.9 (19.6)	–	36.8 (5.8)	32.6 (5.6)	22.9 (18.0)	–	18.6 (16.1)	–
			b	61.3 (6.4)	102.0 (17.1)	–	36.5 (5.7)	36.06 (5.5)	23.5 (15.0)	–	20.2 (13.7)	–
Igelström 2014 [264]	73 M/F	4	a	–	106.6 (19.1)	104.5 (20)	35.2 (5.3)	34.6 (5.7)	–	–	–	–
			b	53.0 (11)	104.8 (18.6)	104.7 (18.5)	33.6 (4.3)	33.5 (4.3)	43.6 (22.2)	–	40.7 (22.4)	–
Johansson 2009[2] [270]	63 M	3	a	47.5 (7.5)	113.4 (14.8)	–	34.4 (2.9)	–	37.0 (17)	–	26.0 (15)	–
			b	49.9 (7.1)	111.7 (13.7)	–	34.8 (2.9)	–	37.0 (14)	–	25.0 (14)	–
Johansson 2011[2] [273]	63 M	NR	c	48.7 (7.3)	113.1 (14.2)	101.0 (14.6)	34.8 (2.9)	31.1 (3.6)	36.0 (15)	19.0 (14)	–	–
Kajaste 2004 [240]	31 M	10	a	50.1 (7.9)	135.3 (16.0)	116.2 (16.3)	42.5 (4.5)	36.6 (5.2)	–	–	47.9 (33.5)	18.3 (17.8)
			b	47.9 (8.0)	145.5 (23.4)	126.3 (27.0)	45.4 (6.2)	39.4 (7.7)	–	–	55.5 (28.5)	29.2 (18.3)
Kemppainen 2008 [274]	52 M/F	0	a	51.0 (8.3)	103.0 (14)	–	33.0 (3.3)	−5.4*[a]	11.0 (3.6)	−3.2 (9.2)[a]	–	–
			b	49.0 (8.9)	94.0 (12)	–	32.0 (3.1)	−0.5*[a]	9.0 (2.7)	−1.3 (5.5)[a]	–	–
Kline 2011 [268]	43 M/F	12	a	47.6 (6.8)	105.6 (15.5)	104.7 (16.1)	35.5 (6.2)	35.15 (6.4)	32.2 (29.1)	24.6 (22.9)	24.5 (21.8)	21.5 (19.2)
			b	45.9 (8.8)	99.3 (20.0)	98.7 (20.0)	33.6 (5.6)	33.46 (6.0)	24.4 (22.4)	28.9 (25.6)	16.8 (16.8)	23.2 (23.2)
Kuna 2013[1] [275]	264 M/F	37	a	61.2 (6.6)	102.8 (19.5)	−5.2 (8.2)[a]	36.8 (5.8)	34.4 (6.1)	22.9 (18)	−4.0 (18.8)[a]	–	–
			b	61.3 (6.4)	101.9 (16.9)	−0.8 (7.8)[a]	36.4 (5.5)	36.1 (5.5)	23.7 (15)	3.7 (17.9)[a]	–	–
Nerfeldt 2008 [266]	20 M	45	a	50.0 (35-69)[b]	113.3 (9.4)	98.5 (9.1)	36.9 (2.6)	32.1 (2.5)	52.3 (19.6)	26.8 (27.8)	57.5 (30.2)	28.0 (32.2)
			b	48 (28-57)[b]	106.8 (11.3)	107.4 (11.3)	33.4 (2.5)	33.6 (2.5	25.2 (22.0)	33.0 (26.2)	33.2 (21.2)	27.4 (16.1)
NG 2015[***] [259]	104 M/F	21	a	51.4 (9.1)	83.7 (15.4)	78.8 (16.3)	30.2 (3.9)	28.4 (4.2)	43.4 (20)	35.3 (21.7)	41.0 (20.3)	30.8 (20.6)
			b	52.0 (9.3)	83.3 (12.2)	81.4 (11.9)	30.5 (4.2)	29.9 (4.2)	42.5 (20)	39.6 (19.5)	40.3 (19.6)	37.7 (19.8)

Papandreou 2012 [276]	40 M/F	0	a	52.2 (10.5)	101.5 (12.5)	−8.9 (3.9)[a]	35.3 (3.8)	−3.2 (1.5)[a]	52.4 (32.8)	−15.6 (11.4)[a]	49.4 (29.9)	−13.1 (9.8)[a]
			b	45.8 (14.2)	108.9 (19.8)	−7.2 (4.2)[a]	37.7 (4.6)	−2.5 (1.4)[a]	58.7 (34.9)	−14.0 (22.6)[a]	56.9 (33.7)	−13.5 (22.6)[a]
Sengul 2011 [269]	20 M	20	a	54.40 (6.6)	86.40 (8.0)	84.7 (9.1)	29.79 (2.7)	29.20 (3.1)	15.19 (5.4)	11.01 (5.3)	–	–
			b	48.0 (7.5)	88.47 (16.2)	88.1 (16.8)	28.42 (5.4)	28.28 (5.5)	17.92 (6.4)	17.36 (11.2)	–	–
Smith 1985 [261]	15 M/F	0	a	58.8 (9.7)	106.2 (28.3)	96.6 (22.9)	–	–	55.0(29.0)**	29.2(27.5)**	–	–
			b	53.3 (5.7)	118.8 (20.9)	120.2 (23.5)	–	–	66.3(23.8)**	70.8(16.1)**	–	–
Tuomilehto 2009[3] [277]	81 M/F	11	a	51.8 (9.0)	101.2 (11.9)	−10.7 (6.5)[a]	33.4 (2.8)	−3.5 (2.1)[a]	10.0 (3.0)	−4.0 (5.6)[a]	–	–
			b	50.9 (8.6)	92.3 (11.3)	−2.4 (5.6)[a]	31.4 (2.7)	−0.8 (2.0)[a]	9.3 (3.0)	0.3 (8.0)[a]	–	–
Tuomilehto 2010[3] [278]	81 M/F	12	a	51.8 (9.0)	100.8 (12.0)	−7.3 (6.5)[a]	33.4 (2.8)	−2.4 (2.1)[a]	10.0 (3.0)	−4.6 (4.9)[a]	–	–
			b	51.7 (8.8)	92.3 (11.4)	−2.9 (7.5)[a]	31.6 (2.8)	−1.0 (2.6)[a]	9.4 (3.0)	−0.5 (9.3)[a]	–	–
Tuomilehto 2013[3] [279]	81 M/F	30	a	51.8 (9.0)	100.8 (12.0)	−5.5 (7.5)[a]	33.4 (2.8)	−1.9 (2.4)[a]	10.0 (3.0)	−0.8 (6.5)[a]	–	–
			b	51.7 (8.8)	92.3 (11.4)	0.6 (8.5)[a]	31.6 (2.8)	0.2 (3.0)[a]	9.4 (3.0)	5.0 (10.9)[a]	–	–

Data provided for a) intervention group, b) control group, and c) whole population.
Data presented as pre- and post-intervention mean (SD), unless otherwise stated; [a] Mean change (SD); [b] Median (range). Dashes (–) indicate outcomes not stated.
AHI, apnoea hypopnoea index; ODI_4, oxygen desaturation index ≥4%/h of sleep.
NR, not reported – The actual drop-out rate is not reported, since participants which dropped out during the study included for the follow-up measurements.
* Standard deviation not reported.
** Non-REM Sleep. REM Sleep mean AHI (events/h) and SD reported as following: At baseline: Intervention= 57.0 (12.3); Control= 48.3 (28.8). After intervention: Intervention= 37.6 (22.0); Control= 48.3 (29.4).
***Data provided by author.
[1,2,3] Superscript numbers identify multiple publications reporting follow-up from one RCT.

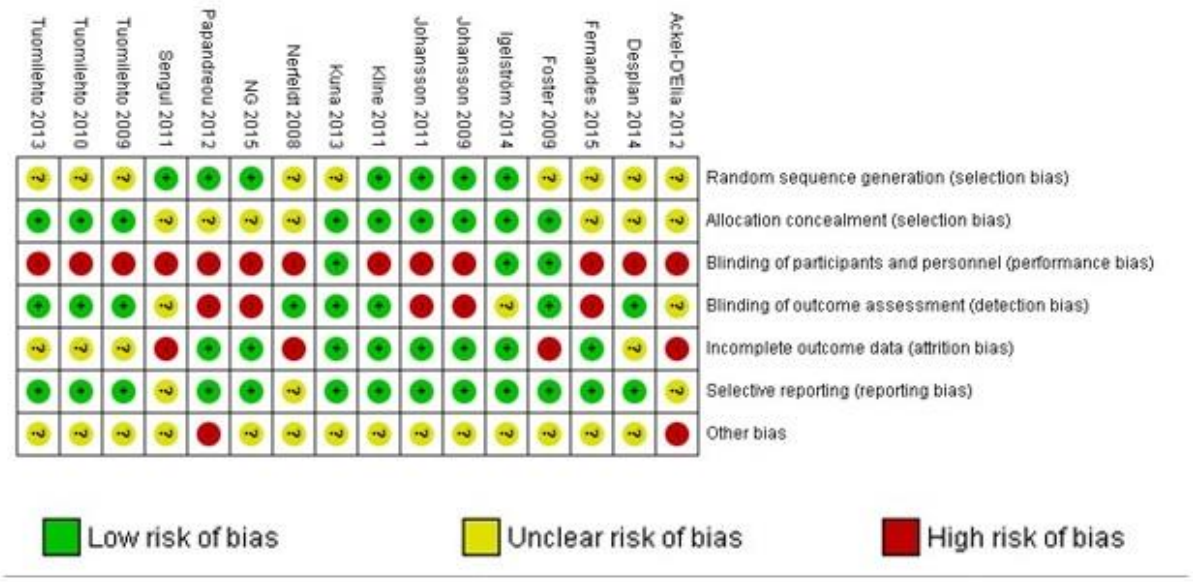


Figure 8. Risk of bias summary for included RCTs in the meta-analyses and follow-up studies; + indicates low risk of bias; – indicates high risk of bias; ? indicates unclear risk of bias.

Overall, the twelve RCTs included in the meta-analyses recruited a total of 755 participants (Intervention group: n=382; Control group: n=373), who underwent lifestyle intervention programs including diet (n studies = 4) (258, 266, 270, 277), exercise (n studies = 3) (265, 268, 269), and/or combination of both (n studies = 5) (24, 259, 264, 267, 276). Each of these studies used different methods in treating control groups (see Table 7). The age of the participants in the studies ranged from 18 – 75 years, with mean baseline AHI ranging from 9.6 to 55.5 events/h and mean baseline BMI ranging from 28.2 to 37 kg/m^2 (Table 1). The timeframe of the intervention varied from one month (267) to one year (24, 259, 277). Three of the included studies in meta-analyses were conducted in Sweden (264, 266, 270), two in the United States (24, 268), and two in Brazil (258, 265), while the remainder of the RCTs were conducted in China (259), France (267), Finland (277), Greece (276), and Turkey (269). Descriptive data for these studies are available in Table 7.

Three of the included RCTs in the meta-analyses (24, 270, 277) followed the long-term effects of their interventions in four separate follow-up studies (273, 275, 278, 279). Two of the follow-up studies by Tuomilehto et al. (278, 279) reported results of the same intervention at different time points (24 months and 60 months). The follow-up studies could not be included in meta-analyses of RCTs to avoid duplication of subjects' data for the same intervention.

Table 7. Study characteristics (12 RCTs included in meta-analyses)

Study	N (a/b)	Population characteristics	Country	Intervention type/length	Detailed description of the intervention
Ackel-D'Elia 2012 [265]	*Randomised 25/22 Analysed 13/19*	*Males; age 25–65 years; BMI < 35* kg/m^2*;* moderate-severe OSA (AHI > 15 events/hr)*; ESS > 9; sedentary; no previous treatment for OSA. Mean (SD): age 49(8.2); BMI 28.3(2.6); AHI 41.6(21.8); 100% male*	*Brazil*	Exercise/ 8 weeks	a) 1 month of sleep hygiene, 2 months of treatment (CPAP + exercise), and 1 week of washout (no treatment). Exercise comprises of 2 months of supervised aerobic exercise, three times/week b) 1 month of sleep hygiene, 2 months of treatment (CPAP), and 1 week of washout (no treatment)
Desplan 2014 [267]	*Randomised 13/13 Analysed 11/11*	*Age 35–70 years; BMI < 40* kg/m^2*;* moderate-severe OSA (AHI > 15 events/hr)*; sedentary (Voorrips activity score < 9); no previous treatment for OSA. Mean (SD): BMI 30.6 (3); AHI 40.2(18.8)*	France	Diet and exercise/ 4 weeks	a) inpatient rehabilitation program, including an individualised exercise training program (24 sessions: 1 session per day; 6 sessions per week during a 4-week period), health education program, and dietary management b) outpatient standard health education program (twice weekly during a 4-week period)
Fernandes 2015 [258]	*Randomised 14/15 Analysed 11/10*	*Age 20–55 years; 40* > BMI ≥ 30 kg/m^2; mild, moderate and severe OSA (*AHI ≥ 5* events/hr*). Mean (SD): age 41.5(9.1); BMI 35.2(2.8); AHI 22.0(46.2); 52 % male*	Brazil	Diet/ 16 weeks	a) energy-restricted diet (ERG): 3347·2 kJ/day (800 kcal/day) reduction in baseline total daily energy expenditure. At weeks 4, 8 and 12, the total energy value of the diet was adjusted according to the participant's body weight at that time b) no changes in food intake
Foster 2009 [24]	*Randomised 125/139 Analysed 125/139*	Age 45–75 years; BMI > 25 kg/m^2; type 2 Diabetes; mild, moderate and severe OSA (AHI ≥ 5 events/hr); no previous surgical or current medical treatment for OSA. Mean (SD): age 61.3(6.5); BMI 36.7(5.7); AHI 23.2(16.5); 41% male	USA	Diet and exercise/ 52 weeks	a) group behavioural weight loss program for type 2 diabetes (intensive lifestyle intervention). Prescribed portion-controlled diets containing 1200- 1500 kcal/day or 1500-1800 kcal/day based baseline weight. Included use of liquid meal replacements and specific snacks for the first 4 months then reduced over subsequent 8 months. Activity prescription of 175 min/week moderate-intensity physical activity b) diabetes management program (3 group session per year), focusing on diet, physical activity and social support
Igelström 2014 [264]	*Randomised 36/37 Analysed 36/37*	Age 18–70 years; BMI ≥ 25 kg/m^2; moderate-severe OSA (AHI > 15 events/hr); insufficient physical activity. Mean (SD): age 55(12); BMI 34.5(4.8); AHI 41.7(20.9); 79.5% male	Sweden	Diet and exercise/ 24 weeks	a) individually tailored behavioural treatment targeting physical activity and eating habits (8-10 sessions), in addition to CPAP treatment b) CPAP treatment and standard care
Johansson 2009 [270]	*Randomised 30/33 Analysed 30/33*	Males; age 30–65 years; BMI 30–40 kg/m^2; moderate to severe OSA (AHI ≥ 15 events/hr); treated with CPAP for > 6 months. Mean (SD): age 49(7.3); BMI 34.6(2.9); AHI 37(15); 100% male	Sweden	Diet/ 9 weeks	a) weight loss through introduction of liquid VLCD: 2.3 MJ/day (550 kcal/day) for 7 weeks to induce ketosis, then gradual introduction of normal foods (total of 6.3 MJ/day (1500 kcal/day) for 2 weeks + group support sessions every 2 weeks b) Wait listed control usual diet (9 weeks) then received the same intervention as above

Kline 2011 [268]	*Randomised 27/16 Analysed 27/16*	Age 18–55 years; BMI ≥ 25 kg/m^2; moderate-severe OSA (AHI ≥ 15 events/hr); no current treatment for OSA; sedentary (< 2 exercise sessions/week). Mean (SD): age 46.9(7.86); BMI 34.8(5.90); AHI 29.3(26.8); 56% male	USA	Exercise/ 12 weeks	a) exercise training: 150 min/week of moderate intensity aerobic activity (4 times/week), followed by resistance training (2 times/week) b) stretching: low-intensity exercises designed to increase whole-body flexibility (2 times/week)
*Nerfeldt 2008** [266]	*Randomised 10/10 Analysed 6/5*	Males; age 20–69 years; BMI ≥ 30 kg/m^2; mild, moderate and severe OSA (AHI ≥ 10 events/hr) and/or ODI ≥ 6; subjective symptoms of OSA. Mean(SD): BMI 35.3(3.1); AHI 40(24.2); 100% male	Sweden	Diet/ 8-week intervention, then crossover	a) weight reduction program including liquid protein drink LCD (800 kcal/day) + group support meetings once/week for a total of 8 weeks, week 7 gradual introduction of low calorie foods b) wait list control usual diet (then received intervention after 8 weeks as above)
NG 2015 [259]	*Randomised 61/43 Analysed 44/37*	Age 30–80 years, BMI > 25 kg/m^2; moderate-severe OSA (AHI > 15 events/hr). Mean(SD): age 51.6(9.14); BMI 30.3(4.0); AHI 43.02(19.9); 75% male	China	Diet and exercise/ 52 weeks	a) dietitian-led lifestyle modification program (LMP) including calorie restriction (10% to 20% energy reduction) + encouraging 30 minutes of aerobic exercise two to three times a week b) simple lifestyle advice from a clinician at baseline and at 6 months
Papandreou 2012 [276]	*Randomised 20/20 Analysed 20/20*	Age 18–65 years; BMI ≥ 30 kg/m^2; moderate-severe OSA (AHI > 15 events/hr); ESS >10. Mean(SD): age 49(12.7); BMI 36.6 (3.7); AHI 55.6(33.6); 85% male	Greece	Diet and exercise/ 24 weeks	a) CPAP therapy + dietitian visits (7 times/6 months), prescribed walking for ≥ 30 min/day + LCD (Mediterranean diet) b) CPAP therapy + dietitian visits (7 times/6 months), prescribed walking for ≥ 30 min/day + LCD (prudent diet)
Sengul 2011 [269]	*Randomised 10/10 Analysed 10/10*	Males; age 40–65 years; mild (5<AHI<15 events/hr) -moderate OSA (16<AHI<30 events/hr) with OSA symptoms. Mean(SD): age 51.2(7.6); BMI 29.1(4.2); AHI 16.55(5.96); 100% male	Turkey	Exercise/ 12 weeks	a) breathing exercise (15–30 min) and aerobic exercises (45–60 min) three times/week for 12 weeks, all given by a single physiotherapist b) routine clinical treatment
Tuomilehto 2009 [277]	*Randomised 40/41 Analysed 35/37*	Age 18–65 years; BMI 28–40 kg/m^2; mild OSA (AHI: 5–15 events/hr). Mean(SD): age 51.3(8.8); BMI 32.4(2.9); AHI 9.6(3.0); 74% male	Finland	Diet/ 52 weeks	a) 1-year supervised lifestyle modification (initial 12-week liquid VLCD, 600-800 kcal/day with low calorie vegetables) followed by low fat (30%) diet tailored for each individual and delivered in 14 group and/or face to face consultations with study nutritionist and physiotherapist) b) one session of general dietary and exercise counseling

N (a/b) = number of participants in group a and b (refer to 'Intervention' column). All studies are RCT – parallel (Level II) as per the NHMRC evidence table **(220)**.
AHI, apnoea hypopnoea index (presented as events per hour); BMI, body mass index (presented as Kg/m^2); ESS, Epworth sleepiness scale; CPAP, continuous positive airway pressure; LCD, low-calorie diet; VLCD, very low-calorie diet.
*Data provided by author.

2.3.2. Effect of lifestyle intervention on OSA severity

A meta-analysis was conducted to assess the differences in mean AHI changes between intervention and control groups and results are outlined in a forest plot (Figure 9). This meta-analysis included eleven studies with n=692 participants, grouped into three subgroups of diet (4 RCTs, 167 participants) (258, 266, 270, 277), exercise (3 RCTs, 95 participants) (265, 268, 269), and combined intervention (4 RCTs, 430 participants) (24, 259, 267, 276). Seven out of 11 studies favoured intervention.

The pooled mean change in AHI was -10.03 events/h (-14.51 to -5.54) and total heterogeneity between all studies was high (Q = 51.57; *df* = 10, P < 0.00001; I^2 = 81%). However, subgroup analysis, detected low levels of heterogeneity within each type of lifestyle intervention (Q = 2.33; *df* = 2, P= 0.31; I^2 = 14.3%). A significant reduction in AHI was observed in diet-only interventions (P= 0.006) and in combined interventions (P= 0.001), however no significant reduction was found in exercise-only interventions (P= 0.17).

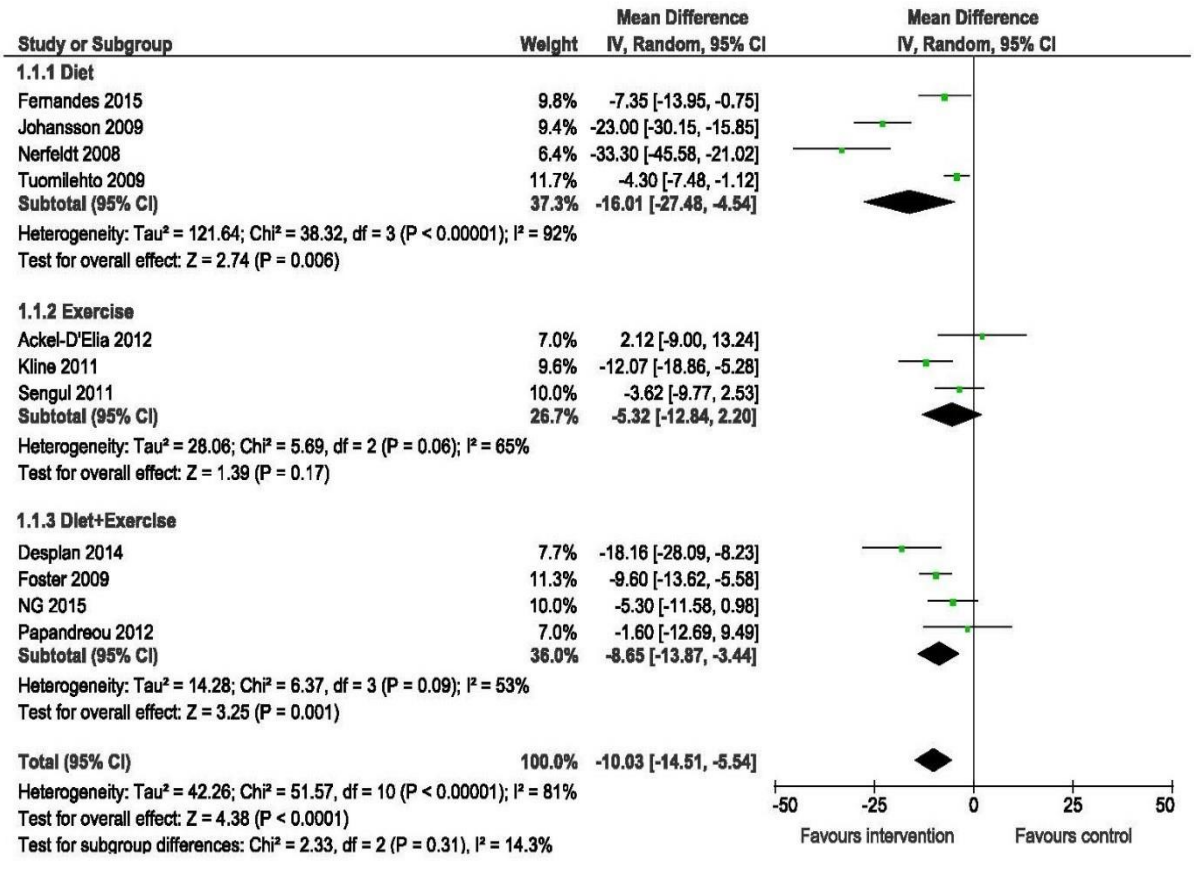


Figure 9. Forest plot of differences in mean AHI (events/h) changes between intervention and control group after intervention in randomised controlled studies using the random-effect model, mean difference and standard deviation. df, degrees of freedom; I^2, I squared, IV, inverse variance method; Random, random effects model; CI, confidence intervals.

2.3.3. Effect of lifestyle intervention on Body Mass Index

A second meta-analysis was conducted to explore the impact of various lifestyle interventions on mean changes in BMI between intervention and control groups (Figure 10). This meta-analysis included 733 participants again grouped into three subgroups: diet intervention (4 RCTs, 167 participants) (258, 266, 270, 277), exercise intervention (2 RCTs, 63 participants) (268, 269), and combined (5 RCTs, 503 participants) (24, 259, 264, 267, 276). The outcome of this meta-analysis is illustrated in a forest plot (Figure 10).

The pooled effect demonstrated that lifestyle interventions, in general were associated with a reduction in BMI. The pooled mean reduction in BMI was -2.08 kg/m^2 (-3.53 to -0.63), with the heterogeneity between studies being very high (Q = 470.46; *df* = 10, P < 0.00001; I^2 = 98%). The test for subgroup differences indicated high heterogeneity within each type of lifestyle intervention (Q = 16.04; *df* = 2, P= 0.0003; I^2 = 87.5%). A significant reduction in BMI was observed in both the diet-only (P < 0.0001) and combined interventions (P= 0.007), but not in the exercise-only intervention (P= 0.43).

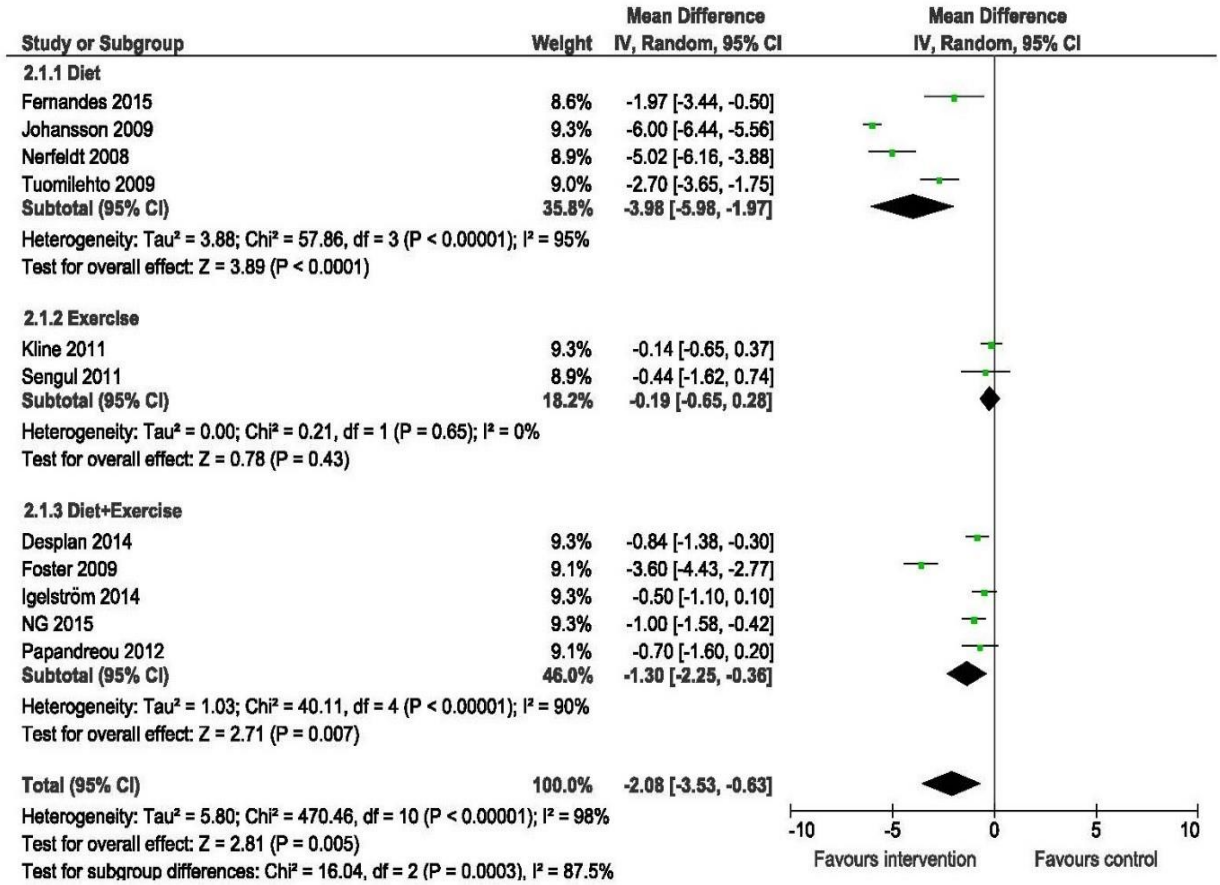


Figure 10. Forest plot of differences in mean BMI (kg/m^2) changes between intervention and control group after intervention in randomised controlled studies using the random-effect model, mean difference and standard deviation. df, degrees of freedom; I^2, I squared, IV, inverse variance method; Random, random effects model; CI, confidence intervals.

2.3.4. Investigation of heterogeneity

To investigate the source of the high levels of heterogeneity in both the BMI and AHI meta-analyses, meta-regression was conducted. The effect of the intervention length, as well as baseline AHI and BMI, on the level of BMI and AHI reduction were investigated in all studies. No significant correlation was observed in any of the investigated potential cofactors (i.e., intervention length, baseline AHI and BMI) and changes in outcomes (i.e., reduction in AHI and BMI).

2.3.5. Potential mechanism of action

A meta-regression to assess the correlation between BMI and AHI changes following the intervention was conducted. This demonstrated that there was a weak yet significant correlation between reduction in AHI and BMI reduction (r= 0.19, p= 0.01; Figure 11).

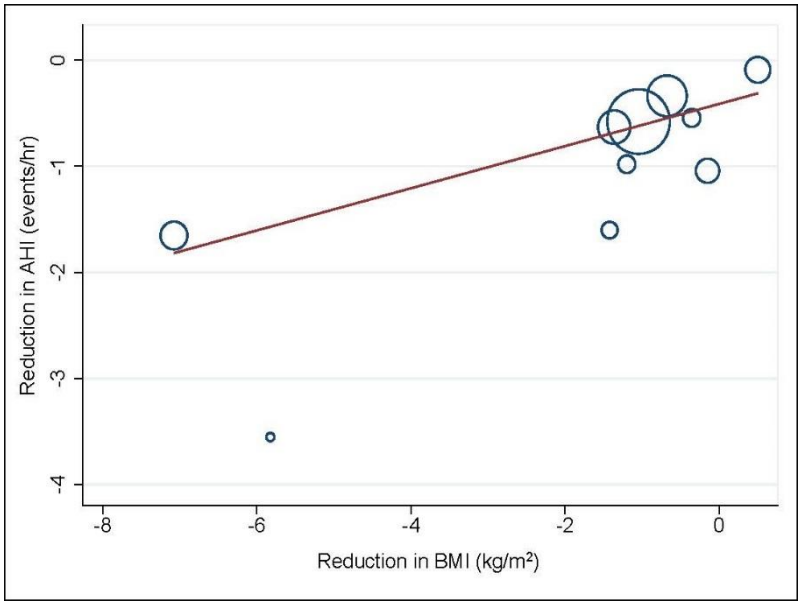


Figure 11. Meta-regression of reduction in BMI against reduction in AHI levels.

2.3.6. Publication bias assessment

Funnel plots are commonly used to visually detect publication bias through identifying the larger random errors in the smaller studies. An asymmetric funnel indicates a relationship between treatment effect estimate and study precision, whereas a symmetrical inverted funnel implies no publication bias (280). In the current study, the effect of the potential publication bias in the findings was assessed separately using two funnel plots. The data presented in funnel plots for AHI and BMI, were reasonably symmetrical (Figure 12 and 13) indicating the lack of publication bias in the results generated from meta-analyses. Even though the absence of publication bias has not been completely confirmed, there was

insufficient evidence for claiming the presence of publication bias. For change in AHI (Figure 12), all data points fall within the funnel. In a funnel plot of BMI changes (Figure 13), there is an outlier on the far left side - referring to the study by Johansson et al. (270). Interestingly, this outlier does not represent the smallest sample size of all studies, yet exhibits a larger effect size in weight loss compared to the other studies.

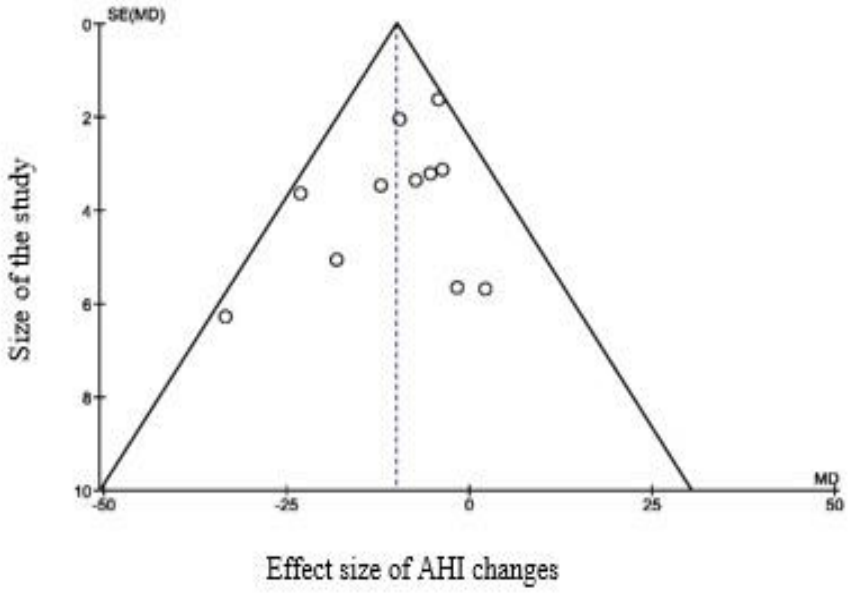


Figure 12. Funnel plot of the intervention effect sizes of AHI changes against size of the study. MD, Mean Difference; SE(MD), Standard Error of the Mean Difference.

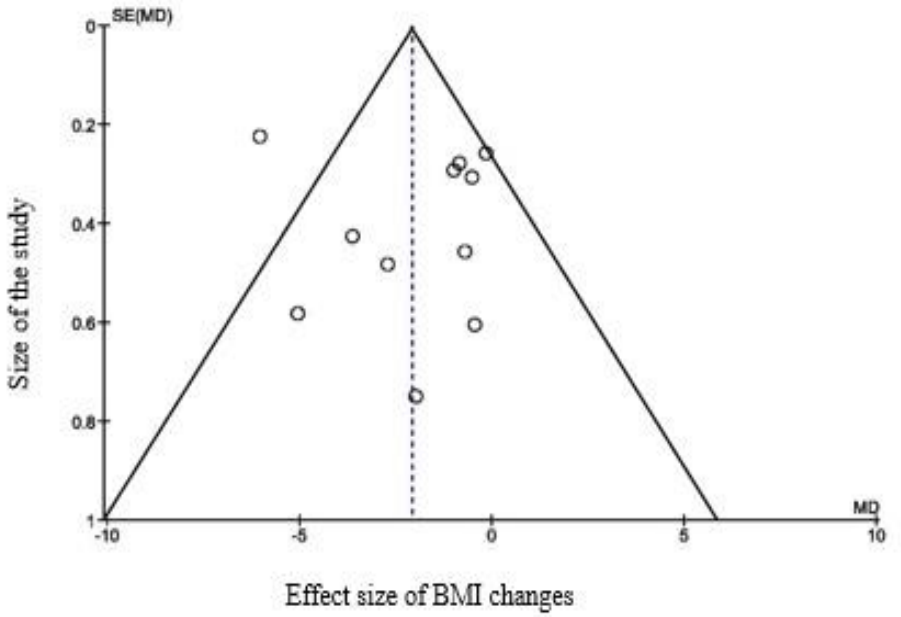


Figure 13. Funnel plot of the intervention effect sizes of BMI changes against size of the study. MD, Mean Difference; SE(MD), Standard Error of the Mean Difference.

2.3.7. Summary of studies not included in meta-analyses

Among seven studies which were not included in meta-analyses, three RCTs involving a diet intervention showed successful weight loss and a decrease in OSA severity (see Table 6) (240, 261, 274). All studies which were not included in meta-analyses, identified weight loss as an initial factor in significant OSA treatment (240, 261, 274).

Among original RCTs not included in meta-analyses, only one study (240) reported up to 16% of cured cases (free of OSA symptoms and the need for therapy), while other RCTs failed to report the proportion of cured cases. From three original RCTs included in the meta-analysis, there were four additional follow up studies which reported long-term effects of different types of lifestyle interventions over 1 (24, 277), 4 (275), and 5 (279) years respectively. Among these, only two (273, 279) reported the proportion of OSA patients who were objectively cured (post-intervention AHI<5 events/hr) after the follow-up assessment. Findings reported in 12-month, 24-month, and 60-month follow-ups, resulted in cure rates in cases versus control of 63% vs. 35% ($p = 0.019$), 57% vs. 31% ($p = 0.032$), and 32% vs. 17% ($p = 0.43$) respectively (277-279). Kuna et al. (275) reported full remission of OSA at year 4 only in participants enrolled with mild baseline OSA, but not in those with moderate-severe baseline OSA. The results revealed improvement, worsening, and remaining the same level of OSA in 43.9%, 20.7%, and 35.4% of cases, respectively (275). Johansson et al. (273), reported a 10% successful treatment of OSA among participants. Details of the follow-up studies and corresponding RCTs can be found in Table 6, 7 and 8.

Table 8. Standardised mean changes in body weight, BMI and AHI over time, intervention versus control (Data extracted from twelve RCTs used in Meta-analyses and their follow-up studies (where applicable))

Study	Intervention /follow-up length		N	Standardised mean Weight	Standardised mean BMI	Standardised mean AHI
Ackel-D'Elia 2012 [265]	baseline–8 weeks		a) 13 b) 19	– –	– –	−5.48 (15.3) −7.60 (16.4)
Desplan 2014 [267]	baseline–4 weeks		a) 11 b) 11	−2.33 (1.7) 0.00 (2.0)	−0.83 (0.6) 0.01 (0.7)	−12.64 (9.6) 5.52 (13.8)
Fernandes 2015 [258]	baseline–16 weeks		a) 11 b) 10	−5.57 (6.0) 0.43 (3.8)	−1.87 (2.0) 0.1 (1.4)	−7.22 (9.3) 0.13 (5.9)
Foster 2009[1] [24]	baseline–52 weeks		a) 125 b) 139	−10.8 (7.8) 0.6 (8.3)	−3.8 (3.4) −0.2 (3.5)	−5.4 (16.8) 4.2 (16.5)
Igelström 2014 [264]	baseline–24 weeks		a) 36 b) 37	−2.1 (4.6) −0.1 (3.3)	−0.6 (1.5) −0.1 (1.1)	– –
Johansson 2009[2] [270]	baseline–9 weeks		a) 30 b) 33	−18.7 (4.1) 1.1 (1.9)	−5.7 (1.1) 0.3 (0.6)	−25 (17) −2 (11)
Johansson 2011[2] [273]	baseline–52 weeks		63	−12.1 (9.0)	−3.7 (2.7)	−17 (16)
*Kline 2011** [19]	baseline–12 weeks		a) 27 b) 16	−0.91 (3.3) −0.57 (1.9)	−0.29 (1.1) −0.15 (0.6)	−7.57 (13.0) 4.5 (9.6)
Kuna 2013[1] [268]	baseline–104 weeks		a) 139 b) 125	−7.4 (7.8) −0.8 (8.3)	– –	−3.8 (17.7) 4.2 (15.7)
	baseline–208 weeks		a) 139 b) 125	−5.2 (7.8) −0.8 (8.3)	– –	−4.0 (18.9) 3.7 (17.9)
Nerfeldt 2008 [266]	baseline–8 weeks		a) 6 b) 5	−14.8 (3.4) 0.6 (2.1)	−4.84 (1.2) 0.18 (0.7)	−25.5 (9.9) 7.8 (10.7)
*Ng 2015** [259]	baseline–16 weeks	completed	a) 44 b) 37	– –	−2.1 (1.4) −0.5 (1.0)	−10.3 (13.5) −0.1 (16.8)
		randomised	a) 61 b) 43	– –	−1.7 (1.5) −0.4 (0.9)	−7.0 (13.1) −0.8 (15.4)
	baseline–52 weeks	completed	a) 44 b) 37	– –	−2.3 (1.7) −0.8 (1.3)	−10.7 (16.7) −3.3 (17.7)
		randomised	a) 61 b) 43	– –	−1.7 (1.7) −0.7 (1.3)	−8.1 (15.5) −2.8 (16.5)
Papandreou 2012 [276]	baseline–24 weeks		a) 20 b) 20	−8.9 (3.9) −7.2 (4.2)	−3.2 (1.5) −2.5 (1.4)	−15.6 (11.4) −14 (22.6)
Sengul 2011 [269]	baseline–12 weeks		a) 10 b) 10	−1.7 (3.9) −0.37 (4.0)	−0.58 (1.4) −0.14 (1.3)	−4.18 (4.4) −0.56 (8.9)
Tuomilehto 2009[3] [277]	baseline–52 weeks		a) 35 b) 37	−10.7 (6.5) −2.4 (5.6)	−3.5 (2.1) −0.8 (2.0)	−4.0 (5.6) 0.3 (8.0)
Tuomilehto 2013[3] [279]	baseline–260 weeks		a) 28 b) 29	−5.5 (7.5) 0.6 (8.5)	−1.9 (2.4) 0.2 (3.0)	−0.8 (6.5) 5.0 (10.9)

Values are presented as mean (SD) change.
N (a/b) = number of participants analysed in a) intervention and b) control group; unless otherwise stated.
AHI, apnoea hypopnoea index; BMI, body mass index; Dashes (–) indicate outcomes not stated.
* Data provided by author.
[1,2,3] Superscript numbers identify multiple publications reporting follow-up from one RCT.

2.4. Discussion

The main findings of this review and the meta-analyses reveal that reductions in energy intake (i.e. diet) when used either alone or in combination with exercise, significantly reduces the level of obesity and OSA severity. By contrast, no such benefit was observed in the small number of exercise-only interventions examined. Furthermore, the effect size of diet-only interventions in reducing AHI and BMI appears to be larger than that of combined interventions. Interestingly, neither baseline BMI, AHI, nor the length of the intervention were associated with changes in AHI or BMI following the interventions. From a clinical perspective, a dietary intervention is the crucial component of any lifestyle-based treatment for overweight adults with OSA. An exercise-based intervention alone is unlikely to confer clinical benefit. While adding exercise to a dietary intervention may give additional health improvements, the available evidence suggests that it would not be expected to improve OSA over and above that achieved by reductions in energy intake alone. The findings from this analysis may help practitioners to direct their advice in treating OSA patients with greater encouragement and support to lose weight using energy restriction.

Although the two (266, 270) studies with the largest reduction in AHI (reduction of -33 and -23 events/hr) also had the largest decrease in BMI (-5 and -6 kg/m^2), our analysis revealed only a very weak, yet significant positive correlation between the reduction in AHI and BMI. This finding is in contrary to the results of a previous meta-analysis by Araghi et al. (251), who failed to find a significant correlation between reduction in AHI and BMI. Interestingly, Araghi et al. (251) reported a positive correlation between baseline AHI and AHI reduction ($r = -0.41$, $p = 0.001$) regardless of the type of intervention introduced, which is in contrast with our analysis showing no significant correlation between these two parameters. Such disparities may be due to the difference in baseline AHI among the participants included in the current and previous meta-analysis (251). Araghi et al. (251) included a larger number of studies with less severity of OSA (7 out of 16 studies with AHI<25 events/hr at baseline) compare to the current study (4 out of 12 studies with AHI<25 events/hr at baseline). There may be number of reasons behind the differences in the outcomes of the studies, which introduced CPAP therapy to OSA patients, including a) a different demographic characteristics of the participants; b) a different baseline AHI (OSA severity level) of the participants; and c) potential weight changes in some of the participants that may have resulted from varied hours of OSA treatment (e.g., CPAP therapy) in some of the studies. Such factors might lead to different levels of weight loss and OSA severity after completing the intervention. For example, for the same amount of reduction in AHI level, those with severe OSA may end up with mild-moderate OSA, whereas mild-moderate OSA may reduce or negate their need for CPAP.

With respect to exercise only interventions, only one (268) out of three included RCTs (265, 268, 269) reported a significant reduction in AHI, whereas no significant reduction in BMI was observed in the two trials that reported BMI findings. The overall analysis of exercise-only

interventions showed no improvement in either BMI or AHI (Figure 9 and 10). Araghi et al. (251) also did not find a significant BMI reduction in exercise-only interventions, however they did demonstrate an improvement in AHI (251). Of note, in that meta-analysis a significant reduction in AHI occurred in one (268) out of two included RCTs (268, 269), but our updated meta-analysis included an additional study which showed no change in AHI, which explains the conflicting results. By contrast, Iftikhar et al. (260) reported a significant association between exercise intervention and reduction in AHI level, as did a recently-published systematic review and meta-analysis by Aiello et al. (281). However, in contrast to the current study which solely included RCTs, both of the systematic reviews by Iftikhar and Aiello included both RCTs and observational studies in their meta-analysis (260, 281). Furthermore, different RCTs have been included in our meta-analysis compared to the ones reported by Aiello et al. and Iftikhar et al. (260, 281). Given that there are conflicting data on the effect of exercise on AHI and BMI, any beneficial effect of exercise on OSA may occur independent of any effect on body weight. In support of this, a study by Netzer et al. (282) showed a beneficial effect of exercise on stabilising muscle tone in the upper airway with a 6-months exercise intervention in moderate-severe OSA patients.

With respect to dietary interventions, the most successful strategies at lowering BMI (reduction of -5 and -6 kg/m^2), applied either an intensive very low-calorie liquid diet (VLCD) or low-calorie liquid diet (LCD) varying between 3.3 kJ/day (266) to 2.3 kJ/day (270) for 8 and 7 weeks, respectively (Table 6). VLCD/LCDs have previously presented numerous metabolic benefits including improvement in concomitant medical problems in obese individuals through rapid weight loss (283, 284). Such improvements were suggested to occur despite the chance of weight regain after discontinuing the diet (283, 284). However, to achieve long-term effects and avoid weight regain, lifestyle alterations via behaviour modification programs are highly recommended (284). By virtue of this, two of our included studies (266, 270) provided regular motivational support sessions and compliance monitoring, besides applying the significant energy restriction. Results from these two studies (266, 270) demonstrated the greatest weighted mean reduction in weight, as presented in a review published by Mitchell et al. (252).

It is of note that seven of the included RCTs (24, 259, 264, 265, 267, 270, 276) used CPAP therapy in combination with lifestyle intervention, whereas others excluded participants with current CPAP treatment. As stated earlier in the introduction (section 2.1), since CPAP induces a small yet significant weight gain (257), the reduction in BMI and AHI may have been attenuated. In our included studies, CPAP therapy may have potentially ameliorated the results achieved from dietary interventions through alterations in metabolism status (285, 286), endocrine function (287, 288), or the proportion of lean/fat mass (289). However, such potential mechanisms would have unlikely altered the final results of our study. Besides, in those studies which used CPAP therapy as part of their intervention, adherence to CPAP was not always reported. Considering the potential effect of CPAP usage on weight changes,

differences in CPAP compliance could have possibly affected unevenly on the outcomes of the weight loss intervention among participants of these studies.

There are several limitations in this meta-analysis which need to be considered. Despite contacting authors to collect unpublished data, we could not manage to obtain all the information required for including studies in the meta-analysis; thus, we had to exclude three of the eligible RCTs (240, 261, 274) from our meta-analysis which might have had the potential to change the results of our analysis. Findings from these two studies, however, were in agreement with the finding from the meta-analysis. There are a small number of exercise-only interventions, compared to a greater body of evidence in diet-only and combined interventions. A small number of studies with exercise-only intervention may potentially have led to a type 2 error in our meta-analysis. There was substantial heterogeneity in inclusion criteria (e.g., previously used /currently using CPAP), baseline characteristics (e.g., both genders versus only males), methodological approach (e.g., different methods used in a certain type of intervention), which impose limits to the generalisability of the results. Intention-to-treat analysis (ITT) was not used consistently in all included studies and that may have partly biased the results. Studies which used ITT analysed all participants who were randomised in the study regardless of their compliance with the treatment, which delivers a more realistic estimate of the efficacy of an intervention in actual clinical practice (290). Studies which did not use ITT are more likely to overestimate the treatment effects of an intervention by only analysing results from participants who successfully finished the study (291). Subgroup analyses within the meta-regression were also not feasible to run due to the limited number of available RCTs under each category of diet, exercise or combination of the two in the current study. Lastly, our study included a limited number of available long-term RCTs (follow up more than 1 year) in the analysis, thus we are only able to reveal the short to medium effect these lifestyle interventions have on BMI and AHI reduction. This highlights the need for future long-term follow-up studies of the effect of lifestyle interventions on AHI and BMI.

In conclusion, dietary based interventions (with or without exercise) are more effective at improving OSA than exercise only interventions. Thus, dietary interventions with significant energy restriction need to be an essential component of ‘lifestyle’ treatment for OSA. While increasing exercise may confer health benefits they would not be expected to improve OSA over and above achievements from dietary changes alone. Furthermore, future long-term studies are required to determine whether other factors such as the timing of the lifestyle intervention (in combination with CPAP therapy) influence treatment outcomes.

Chapter 3: Exploring the relationships between OSA severity, eating behaviour, anxiety and depression levels in adults newly-diagnosed with OSA

3.1. Introduction

Obstructive sleep apnoea (OSA) is associated with many physiological and mental health consequences, including obesity, cardiovascular disease, metabolic syndrome, anxiety and depression (5, 97, 186, 292). Common symptoms of OSA include poor sleep quality, daytime sleepiness, lack of energy, and behavioural/mood changes (7-12, 293). OSA severity is classified based on the cut-offs defined by the American Academy of Sleep Medicine (AASM) (see Table 2). By virtue of this, it may seem reasonable to expect that a greater OSA severity is associated with greater severity of common co-morbidities in OSA population (e.g., anxiety and depression). However, such an assumption remains controversial based on the current evidence. For instance, many studies have found associations between anxiety/depression and the presence of OSA (96, 97, 193, 194, 294). Such findings might explain why patients with a higher severity of OSA are more likely to have an increased incidence of anxiety/depression. However, OSA severity could not explain the increase in anxiety and depression levels in two other studies (192, 295). Importantly, both studies demonstrating the lack of relationship between OSA severity and anxiety/depression levels, a) used different measurement tools for assessing levels of anxiety and depression, and b) failed to take into consideration the potential effect of factors (e.g., eating behaviour) that may be related to both OSA-accompanying factors (e.g., obesity), and anxiety/depression levels. Thus, the current study sought to respond to a necessity for (a) investigating the relationship between OSA severity and levels of associated symptoms to confirm if previous findings were replicable and robust, and (b) assessing the relationship between OSA severity and potential underlying factors that may have affected the relationship between OSA severity and levels of anxiety and depression.

Anxiety and depression occur in approximately 14.4% and 4.1% of the Australian population aged 16-85 years, respectively (296). Obesity and anxiety/depression are very common co-morbidities in patients with OSA (186, 297). Many studies suggest that overweight and obesity are positively associated with higher risk of developing anxiety and depression, independent of OSA (122, 202-206). Further evidence have reported that there are various additional interacting factors involved in promoting weight gain/obesity including an individual's genetic make-up, environment, and importantly eating behaviours (298, 299). Evaluation of eating behaviour usually is done by using the three-factor eating behaviour questionnaire (TFEQ) or its shortened version (TFEQ-R18) which evaluates three aspects of cognitive restraint, uncontrolled eating, and emotional eating (154, 300) (see Appendix 5). Alterations in eating behaviour may occur through sleep disturbances and poor sleep quality, which are commonly seen in OSA patients. Sleep disturbances in non-OSA populations may promote elevated calorie intake (301), behavioural alterations (tendency for consuming foods

with high fat and carbohydrate content) (253, 302), changes in metabolism (decreases in resting metabolic rate) (149), and hormonal variations (i.e., decreases in satiety hormone (leptin) and increases in hunger-stimulating hormone (ghrelin)) (149), possibly leading to weight gain and/or difficulty in losing weight (303). It is not known whether the same holds true for OSA population. Moreover, poor sleep quality may be associated with greater BMI via increased disinhibited eating behaviour (responsiveness to food stimuli such as the sight or smell of food), when assessed using the TFEQ questionnaire (304). Furthermore, related comorbidities such as anxiety and depression may contribute to changes in eating behaviour and consequently weight gain (305). OSA patients may experience alterations in appetite-regulating hormones, leading to an increased appetite and elevated energy intake (303). Such mechanisms may lead to a modified eating behaviour, changes in meal timing, quantity of food consumed and food preferences. However, no evidence have investigated (a) the possible effect of eating behaviour in developing obesity in patients with OSA, (b) the potential relationship between anxiety/depression and eating behaviour in patients with OSA.

To date, a limited number of studies have demonstrated a positive association of CPAP therapy with weight gain/obesity (238, 285, 306). Moreover, CPAP treatment is suggested to lead to a reduced level of anxiety and depression (96, 194, 237, 307), which may alter the effect that anxiety/depression might have had on obesity in non-treated OSA patients. Therefore, when investigating the association of OSA severity and related comorbidities, it is important to only assess newly-diagnosed OSA patients, in order to eliminate potential effects of OSA treatment on the results.

So far, only one study by Macey et al. (308) examined the association of OSA severity and anxiety/depression in newly-diagnosed OSA patients living in USA. This study found no direct association between severity of OSA and levels of anxiety and depression (308). In this study, the severity of anxiety and depression was measured using the Beck anxiety inventory (BAI) and the Beck depression inventory-second version (BDI-II), respectively (308) which are subjective questionnaires. So far, there is no gold-standard objective measurement to determine severity levels of anxiety/depression. However, it is worthwhile re-examining the association between OSA severity and levels of anxiety/depression in a sample of residents living in Australia, with using other subjective psychological measurement tools (e.g., HADS questionnaire) and see if the results are comparable to those reported by Macey et al. (308).

The main objective of this study was to examine the relationship between anxiety/depression scores from the BDI-II and the HADS questionnaire. Moreover, to explore the relationships between OSA severity, and three aspects of eating behaviour (i.e., cognitive restraint, uncontrolled eating, and emotional eating), levels of anxiety and depression and BMI in overweight and obese adults who are newly diagnosed with moderate-severe OSA.

More specifically, we aimed to:

1. Examine the relationship between depression scores generated from the HADS and the BDI-II questionnaire.
2. Assess the relationships between OSA severity (as assessed by the AHI) and (a) BMI, (b) three aspects of eating behaviour, (c) anxiety and depression.
3. Evaluate the relationships between a number of demographic variables and eating behaviours (i.e., gender, age, BMI, cognitive restraint, uncontrolled eating, emotional eating), with the levels of anxiety and depression.

The following hypotheses were tested:

1. There will be a positive relationship between depression scores resulting from the HADS and the BDI-II questionnaires.
2. Increasing OSA severity (i.e. higher AHI) will be associated with greater BMI, higher scores in cognitive, uncontrolled, and emotional eating AND of anxiety and depression.
3. Higher scores in cognitive restraint/uncontrolled eating/emotional eating AND greater levels of anxiety and depression will be associated with female gender, advanced age, and greater BMI. Increased scores in cognitive restraint/uncontrolled eating/emotional eating will be associated with enhanced levels of anxiety and depression.

3.2. Methods

Declaration of my role in conducting the sleeping well trial and preparing this chapter:

I was study coordinator for the sleeping well trial. My role was to coordinate the study procedure through contacting potential participants, recruiting participants, scheduling monthly visits for the participants, preparing nutrition packs for the dietician sessions, setting up monthly meetings with the study team to discuss potential issues and required amendments to the study protocol, performing participants' anthropometric measurements, and collecting participants' blood samples. Furthermore, my role included data collection via using questionnaires and securing the collected data, as well as data analysis. Throughout the experiments, I mediated between all parties involved, resolved the upcoming problems and made sure that the sleeping well trials proceeded smoothly.

3.2.1. Study overview

This study utilised data collected as part of baseline data collection gathered by the study coordinator (myself) from the participants who enrolled in The Sleeping Well Trial during March 2016 to May 2017.

The Sleeping Well Trial was a randomised controlled trial, designed to reveal a potential ideal time to introduce lifestyle (weight management) intervention for CPAP users with an aim to maximise weight loss, and reduce the severity of OSA. The Sleeping Well Trial has been registered at the Australian New Zealand clinical trials registry (ANZCTR) (Trial registration ID: ACTRN12616000203459; valid from: 16/02/2016). This study was performed in accordance with The Sleeping Well Trial protocol study (Appendix 2) approved by Monash Health Human Research Ethics Committee (HREC/15/MonH/93; valid from: 20/10/2015) (Appendix 3). Written informed consent was obtained from each participant before conducting the data collection (Appendix 4).

3.2.1.1. Screening procedure

Participants were identified during routine attendance at one of two collaborating sleep clinics in Melbourne; Monash Health and Eastern Health. Sleep physicians informed the study coordinator of the list of the potential participants based on their sleep study results. Participants were contacted via phone and their eligibility for inclusion in the study was assessed by the study coordinator (myself). If the participants met the inclusion criteria described in Table 9, they were invited to attend a further screening session.

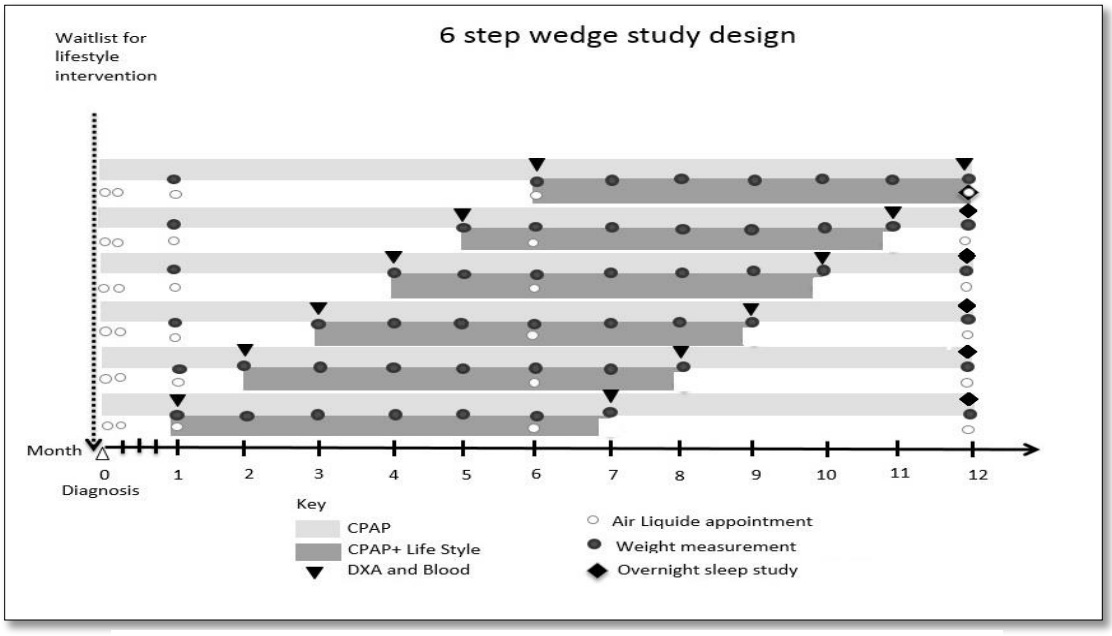


Figure 14. The sleeping well trial – stepped wedge design

Table 9. The sleeping well trial – eligibility requirements

Inclusion criteria	Exclusion criteria
1. Adults aged 19-68 years 2. Moderate-severe untreated OSA (AHI≥ 20 events/hr, based on the AASM alternate criteria) 3. Overweight/obese (Asian and Indian heritage participants with a BMI from 23 to 43 kg/m^2 and other heritage BMI range 25 to 43 kg/m^2) 4. Sedentary (self-reported exercise < 2 days/week and ≤ 45 minutes per session) 5. Required and eligible to use fixed-pressure continuous positive airway pressure (CPAP)	1. Pregnant women 2. Diagnosed with concomitant obesity hypoventilation syndrome 3. Diagnosed with diabetes type 1 or 2 (if on insulin treatment) 4. Severe psychiatric disorder 5. Drowsiness 6. Commercial drivers 7. Required to use "VPAP" or "BPAP" (variable/bilevel positive airway pressure) 8. Inability to exercise (e.g. Due to orthopedic or musculoskeletal problems) 9. Previous surgical or current medical treatment for OSA 10. Previous Bariatric surgery 11. Current use of weight loss weight loss programs and/or weight loss drugs 12. Recent Angina Pectoris or atrial fibrillation 13. Allergic to cow's milk protein 14. Insufficient knowledge of English language 15. Unable to provide informed consent

Polysomnography (PSG)

An in-laboratory overnight sleep study had been undertaken prior to participating in this study. Sleep studies were ordered by the treating sleep physicians at Monash Health or Eastern Health. This procedure was a part of the patient's routine care and performed regardless of patient's participation in this study.

Polysomnography (PSG) was used as a diagnostic tool for identifying OSA and its level of severity. PSGs were scored manually for sleep stages and respiratory events. Each episode of apnoea and hypopnoea was identified based on the recommended criteria for scoring of sleep and associated events published by American Academy of Sleep Medicine (AASM) (2012) (309). Accordingly, apnoeas were defined by the absence of airflow that lasted for more than 10 seconds in the presence of continued respiratory effort, and hypopnoeas were identified as reduction in airflow of equal or greater than 30% of resting levels, lasting for ≥ 10 seconds occurring either with ≥ 3% oxygen desaturation or an associated arousal.

The presence of arousal was identified using an electroencephalogram (EEG) which measures brain activity during sleep. The information regarding AHI levels were extracted from the sleep study reports and considered as eligibility criteria. OSA was classified into three severity levels of mild (AHI: 5-14 events/hr), moderate (AHI: 15-30 events/hr), and severe (AHI≥30 events/hr). Total AHI of equal or more than 20 events per hour was used to identify those with moderate and severe OSA to be contacted for the purpose of this study (see inclusion criteria outlined in Table 9).

3.2.1.2. Data collection procedure

Participants were invited to a baseline session for "The Sleeping Well Trial" at Be Active Sleep & Eat (BASE) facility in Notting Hill. Participants underwent weight and height measurement to confirm their eligibility. Once eligibility was confirmed, full informed written consent was obtained. By opening a sealed envelope in the presence of each participant, which contained a pre-determined and concealed wait list period, they were informed of their assigned wait period based on the randomised number of months written in the envelope. Participants were asked to provide their personal information, demographic characteristics, and reports on their current drug therapy (i.e., anti-hypertensives and anti-depressants) in a self-reported data collection sheet. Participants were asked to identify their ethnicity from 5 categories: Asian, Caucasian, Indian, mixed-race, or other. Participants underwent blood pressure measurement and thereafter, samples of their blood were collected. Participants were asked to respond a series of questionnaires regarding their sleep, health, physical activity, quality of life, eating behaviour, and anxiety/depression symptoms. At the end of the baseline session, participants were referred to a CPAP clinic to receive a CPAP machine, a fitted mask, and instructions to commence CPAP therapy. Participants' enrolment, anthropometric measurements, blood collection and referral to a CPAP clinic were conducted by the study coordinator (myself).

3.2.2. Measures

Questionnaires about eating behaviour, and symptoms of depression and anxiety were answered via software (Qualtrics) using an iPad with a link to the questionnaire) which automatically saved the participants' responses in the system for later analysis. This procedure was done in the presence of one of the study team members. All of the measurements and data collection for the purpose of this analysis were taken during the initial visit.

3.2.2.1. Body mass index

Height and weight measurements were conducted based on the anthropometry procedures manual provided by Centres for Disease Control and Prevention (91).

Participants were asked to remove their shoes and heavy clothing, stand on the scale while looking forward. Weight were recorded twice to the nearest 0.1 kg using an electronic flat scale (Seca 803). When the two weight measurements disagreed by more than 1 kg, a third measurement was taken. All the measurements were recorded in the data collection sheet and the mean of the two closest measurements was calculated and entered into the database.

Height was measured with a wall-mounted Holtain stadiometer. Participants were asked to remove their shoes and stand with their heels together. Height was recorded while heels, buttocks and shoulders were placed against the wall, and arms set by their sides with the palms against the thighs. Height was measured twice to the nearest 0.1 cm and recorded in the data collection sheet. The mean of the two height measurements were calculated and entered into the database.

BMI was calculated using the formula (weight (kg)/height (m^2)). Participants who were overweight (Asian and Indian heritage participants with a BMI from 23 kg/m^2 to 43 kg/m^2 and other heritage BMI range of 25 kg/m^2 to 43 kg/m^2) identified as eligible to participate in this study. The lower range BMI for participants with Asian and Indian origin has been set from 23 kg/m^2 to enable participants of Asian and Indian origin who have increased cardiovascular risk at a lower BMI than Caucasians to be included in the study (263, 310, 311). The upper range of BMI for all participants has been set to 43 kg/m^2 to include adults with high cardiovascular disease risk to be included in the study.

3.2.2.2. Blood pressure

Blood pressure was measured using a digital blood pressure device (Welch Allyn ProBP 3400). Participants were asked to sit comfortably for at least five minutes before recording the first blood pressure measurement. Blood pressure was measured on the right arm using a cuff size appropriate to the arm circumference (cuff size 11 for adults, arm circumference: 25.0 – 34.0 cm; cuff size 12 for large adults, arm circumference: 32.0 – 43.0 cm) measured at midway between the elbow and shoulder. The bottom of the cuff was placed at least 3 cm above the elbow crease. Participants were asked to place their arm on the desk with the elbow approximately level with the heart. When measurement completed, device displayed systolic and diastolic blood pressure. Two readings with at least a 1-minute interval was performed and measurements were recorded in the data collection sheet. The mean of the two observations were calculated and entered into the database.

3.2.2.3. 18-item Three-Factor Eating Behaviour Questionnaire (TFEQ-R18)

Eating behaviour was measured using a self-rated 18-item three-factor eating behaviour questionnaire (TFEQ-R18) (Appendix 5) and is considered a valid and reliable tool to be used in distinguishing different eating patterns in adult population (154, 312).

The TFEQ-R18 comprises 18 items to assess three dimensions of eating behaviour including cognitive restraint (6 items), uncontrolled eating (9 items), and emotional eating (3 items) (154, 312). Cognitive restraint questions have been used to address the tendency to restrict food intake in individuals in order to control their weight and body shape. Uncontrolled eating refers to overeating as a result of lack of control over eating. Emotional eating assess the state where a large quantities of food is being consumed in response to an emotional trigger rather than an actual physical hunger (312).

Each question/item contained within the TFEQ-R18 is rated on a 4-point scale (1 = "Definitely true", 2 = "Mostly true", 3 = "Mostly false", 4 = "Definitely false"), with a theoretical ranges of 6 –24, 9 –36, and 3–12 for cognitive restraint, uncontrolled eating, and emotional eating respectively. The raw scale scores in each dimension are transformed to a 0–100 scale to generate the total score for each dimension, where the higher total score for each dimension indicates a greater relevant level of restrained, uncontrolled, or emotional eating.

3.2.2.4. Hospital Anxiety and Depression Score (HADS)

Anxiety and depression symptoms were measured using a self-reported hospital anxiety and depression score (HADS) (Appendix 6) which is known as a valid and reliable tool to identify non-physical symptoms of anxiety and depression in the general population and primary care medical practice (180, 184).

Seven items in the HADS questionnaire are related to anxiety with the remaining seven items related to depression levels (183). Responses to each item in the questionnaire is being scored on a scale of 0-3, where a score of "3" represents higher symptom frequencies (313). Each subscale (depression or anxiety) scores will be generated by obtaining the sum of scores in that particular subscale, ranging from 0 to 21. The scores from each subscale is graded into three levels of severity (see Table 5). A cut-off point of 8 out of 21 scores for each subscale is used for identifying anxiety or depression in an individual (180). A total score for the entire HADS questionnaire reflects the level of emotional distress, ranging from 0 to 42, where higher scores indicating more distress (183).

3.2.2.5. Beck Depression Inventory-second version (BDI-II)

Beck Depression Inventory-II (BDI-II) was used to measure depression symptoms severity (Appendix 7), which is considered a valid and reliable tool to measure intensity of physical and non-physical depressive symptoms experienced in psychiatric and normal population (96, 185).

Each question in BDI-II can be answered with four possible responses scored from 0 to 3, where "3" indicates higher symptom severity. A total score is then generated by obtaining the sum of scores given to each question in BDI-II, where higher scores indicates more severe

depressive symptoms. In the general population (96), a total score in BDI-II is used to categorise depressive symptoms into four levels of severity (see Table 5).

3.2.3. Statistical analysis

All statistical analyses were performed using SPSS version 24 for Windows (SPSS Inc., Chicago IL, USA) and p-values less than 0.05 were regarded as statistically significant. For the purpose of analyses in the current study, p-values equal or more than 0.5 and less than 0.10 were considered as a trend.

Aim 1: Pearson's correlation analysis was carried out to examine the existence and strength of the relationship between the two depression levels yielded from the HADS and the BDI-II questionnaire.

Aim 2: A goodness of the fit test was applied and the best model (linear regression) was selected. Linear regression was used to separately investigate the relationships between OSA severity as an independent variable and each of the dependent variables; i.e., cognitive restraint, uncontrolled eating, emotional eating, anxiety and depression.

Since the majority of the correlations did not meet the statistical significance threshold of 0.05, applying a multiple linear regression was not considered feasible in our analyses. Thus, association analyses were conducted using univariate linear regression.

Aim 3: Linear regression was conducted to separately evaluate the associations between independent variables (i.e., gender, age, BMI, cognitive restraint, uncontrolled eating, and emotional eating) and dependant variables (i.e., anxiety and depression levels from the BDI-II and HADS questionnaires).
Linear regression was used to separately explore the relationships between independent variables (i.e., gender, age, BMI) and the dependant variable (i.e., cognitive restraint). The same analyses were conducted with including the same independent variables and replacing the dependent variable (i.e., cognitive restraint), firstly with uncontrolled eating, and secondly with emotional eating.

3.3. Results

3.3.1. Overview

The study included 60 participants, in which 31 and 29 participants were recruited from Box Hill Hospital and Monash Medical Centre, respectively.

Descriptive statistics were used to describe sample characteristics, in which continuous variables were reported as mean and standard deviation, and categorical data were reported as absolute and relative frequencies (Table 10). Participants' demographic characteristics, anthropometric measurements, blood pressure, OSA severity, and current use of drugs (i.e., anti-hypertensive agents and anti-depressant medication) are shown in Table 10.

The mean age of the participants was 50.18 ± 10.74 years (ranging from 24-69 years), with the majority being male (73% male) with 30% having moderate OSA and 70% with severe OSA. The group was primarily Caucasian (60%), while the remaining participants were Asian (8%), Indian (8%), mixed-race (5%), or from other races (18%). Participants had a mean neck and waist circumference of 42.56±4.09 and 112.55±12.72 cm, respectively. The mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) were 134.05±15.20 mmHg and 86.78±12.33 mmHg, respectively.

At the time of data collection, 20% of the participants reported being treated with anti-depressants either for depression or for anxiety. Fourteen out of 60 participants (23%) were being treated with anti-hypertension medication at the time of data collection.

Results of the psychometric questionnaires (the HADS and the BDI-II questionnaire) were expressed by mean and standard deviation. Proportion of the participants across all anxiety/depression severity levels were reported as frequency and percentage (Table 11). Results of the TFEQ-R18 questionnaire were illustrated by mean and standard deviation for the three aspects of eating behaviour (i.e., cognitive restraint, uncontrolled eating, and emotional eating) (Table 11). Participants had a mean score of 16.93±2.30, 23.60±3.72, and 8.42±2.68 for cognitive restraint, uncontrolled eating and emotional eating, respectively. On average, participants had a mean score of 34.88±9.60 for depression in the BDI-II questionnaire and a mean score of 18.07±2.97 and 14.92±1.77 for anxiety and depression from the HADS questionnaire, representing a moderately anxious and depressed population.

Table 10. Baseline characteristics of the participants enrolled in the sleeping well trial

Characteristics (n=60)	**Mean SD**
Age (years)	50.18 ± 10.74
Gender ▪ Male ▪ Female	 44 (73%) 16 (27%)
Ethnicity ▪ Asian ▪ Caucasian ▪ Indian ▪ Mixed-race ▪ Other	 5 (8%) 36 (60%) 5 (8%) 3 (5%) 11 (18%)
Anthropometric measurements	
BMI (kg/m^2)	34.26 ± 4.6 (25.7–43)
Neck circumference (cm)	42.56 ± 4.09 (34.25–51.45)
Waist circumference (cm)	112.55 ± 12.72 (87.5–140.75)
Sleep	
AHI (events/hour)	46.85 ± 21.14
OSA severity ▪ Moderate OSA (15≤AHI<30) ▪ Severe OSA (AHI≥30)	 18 (30%) 42 (70%)
Blood pressure	
SBP (mmHg)	134.05 ± 15.2
DBP (mmHg)	86.78 ± 12.33
Current drug therapy	
Anti-depressant use	12 (20%)
Anti-hypertensive use	14 (23%)

Abbreviations: BMI, body mass index; kg/m^2, kilograms per square meter; AHI, apnoea-hypopnoea index; OSA, obstructive sleep apnoea; SBP, systolic blood pressure; DBP, diastolic blood pressure; mmHg, millimetres of mercury.

Data are presented as mean ± SD, and range or number (%) as appropriate.

Percentages are rounded to zero decimal place. All other figures are rounded to the second decimal place.

Table 11. Baseline psychometric and eating behaviour results of the participants enrolled in the sleeping well trial

Anxiety and depression	
Emotional distress - HADS (total score)	18.98 ± 3.51
Anxiety score	11.07 ± 2.97
▪ No anxiety	9 (15%)
▪ Mild	13 (22%)
▪ Moderate	31 (52%)
▪ Severe	7 (12%)
Depression score	7.92 ± 1.77
▪ No depression	25 (42%)
▪ Mild	29 (48%)
▪ Moderate	6 (10%)
▪ Severe	0
BDI-II	34.88 ± 9.61
▪ No depression	0
▪ Mild	0
▪ Moderate	16 (27%)
▪ Severe	44 (73%)
Eating behaviour	
TFEQ-18	
▪ Cognitive eating	16.93 ± 2.3
▪ Uncontrolled eating	23.6 ± 3.72
▪ Emotional eating	8.42 ± 2.68

Abbreviations: HADS, hospital anxiety and depression scale; BDI-II, Beck depression inventory-second version; TFEQ-R18, 18-item three-factor eating behaviour questionnaire.
Data are presented as mean ± SD, and number (%) as appropriate.
Percentages are rounded to zero decimal place. All other figures are rounded to the second decimal place.

3.3.2. Main analyses

Aim 1:

- Correlation between depression scores from the HADS and the BDI-II questionnaire

The depression component of the HADS questionnaire was significantly correlated (albeit weakly) with the score determined from the BDI-II (r^2=0.13, p<0.01) (See Figure 15).

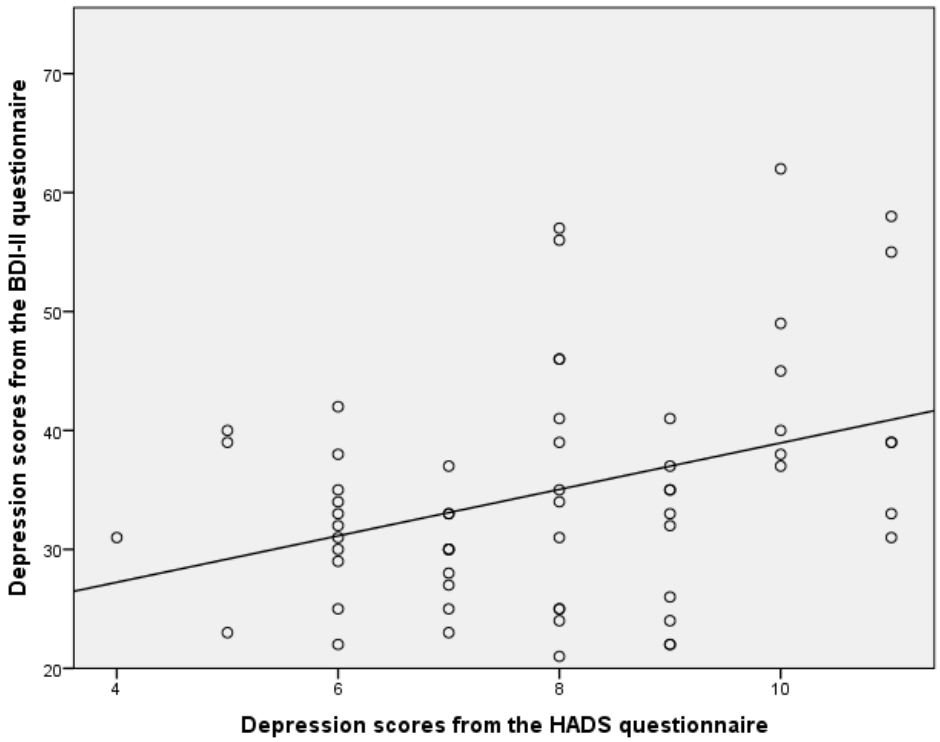


Figure 15. The scatter plot of the correlation between depression scores generated from the HADS and BDI-II questionnaires. The scatter plot provides a visual picture of a weak, yet positive correlation (r^2=0.13, p<0.01) between depression scores from the HADS and the BDI-II questionnaire.

Aim 2:

- Relationships between OSA severity (as assessed by the AHI) and BMI

A significant negative association was found between OSA severity and BMI level (β= -0.23, 95% CI [-0.44, -0.03], p= 0.03).

- Relationships between OSA severity (as assessed by the AHI) and three aspects of eating behaviour

OSA severity was not associated with either uncontrolled eating (β = -0.02, 95% CI [-0.07, 0.02], p= 0.32), nor cognitive restraint (β= 0, 95% CI [-0.03, 0.03], p= 0.78). A negative trend was found between OSA severity and emotional eating, however this just failed to reach statistical significance (β= -0.03, 95% CI [-0.06, 0], p= 0.06).

- Relationships between OSA severity (as assessed by the AHI) and levels of anxiety and depression

OSA severity was not associated with anxiety (β= 0.01, 95% CI [-0.03, 0.05], p= 0.58), and depression levels from either the BDI-II (β = 0.08, 95% CI [-0.03, 0.20], p= 0.16) or HADS questionnaires (β= 0.02, 95% CI [0, 0.04], p= 0.18).

Aim 3:

- Associations between a number of demographic variables and eating behaviours (i.e., gender, age, BMI, cognitive restraint, uncontrolled eating, emotional eating), with the levels of depression (results from the BDI-II questionnaire)

Depression level (determined using the BDI-II questionnaire) was not significantly associated with gender (β= 0.84, 95% CI [-4.82, 6.50], p= 0.77), age (β= 0.04, 95% CI [-0.20, 0.28], p= 0.74), BMI (β= -0.04, 95% CI [-0.59, 0.50], p= 0.87), cognitive restraint (β= -0.35, 95% CI [-1.45, 0.74], p= 0.52), and uncontrolled eating (β= -0.19, 95% CI [-0.87, 0.49], p= 0.58). A trend was observed between higher depression levels and lower scores in emotional eating, however this failed to reach statistical significance (β= -0.77, 95% CI [-1.69, 0.15], p= 0.10).

- Associations between a number of demographic variables and eating behaviours (i.e., gender, age, BMI, cognitive restraint, uncontrolled eating, emotional eating), with the levels of depression (results from the HADS questionnaire)

Depression level (determined using the HADS questionnaire) was not significantly associated with gender (β= -0.4, 95% CI [-1.44, 0.64], p= 0.45), age (β= -0.01, 95% CI [-0.05, 0.03], p= 0.62), BMI (β= -0.02, 95% CI [-0.13, 0.08], p= 0.64), uncontrolled eating (β= 0.03, 95% CI [-0.09, 0.16], p= 0.59) and emotional eating (β= 0.05, 95% CI [-0.13, 0.22], p= 0.61). A trend was observed between higher depression level and lower scores in cognitive restraint, however this failed to reach statistical significance (β= -0.17, 95% CI [-0.37, 0.03], p= 0.09).

- Associations between a number of demographic variables and eating behaviours (i.e., gender, age, BMI, cognitive restraint, uncontrolled eating, emotional eating), with the levels of anxiety

Anxiety level was not significantly associated with gender (β= -0.52, 95% CI [-2.26, 1.23], p= 0.56), age (β= -0.02, 95% CI [-0.09, 0.06], p= 0.67), BMI (β= 0.03, 95% CI [-0.15, 0.20], p= 0.77), cognitive restraint (β= 0.14, 95% CI [-0.2, 0.48], p= 0.40), uncontrolled eating (β= 0.17, 95% CI [-0.04, 0.37], p= 0.11). A trend was observed between higher anxiety level and greater scores in emotional eating, however this just failed to reach statistical significance (β= 0.27, 95% CI [-0.02, 0.55], p= 0.07).

- Associations between a number of demographic variables (i.e., gender, age, BMI), with three aspects of eating behaviours (i.e., cognitive restraint, uncontrolled eating, emotional eating)

Cognitive restraint was not significantly associated with gender (β= -0.34, 95% CI [-1.69, 1.02], p= 0.62), age (β= -0.03, 95% CI [-0.08, 0.03], p= 0.34), and BMI (β= 0.09, 95% CI [-0.04, 0.22], p= 0.17). Uncontrolled eating was not significantly associated with gender (β= 1.82, 95% CI [-0.32, 3.97], p= 0.09), age (β= 0.02, 95% CI [-0.07, 0.11], p= 0.68). Greater uncontrolled eating was significantly associated with lower BMI (β= -0.23, 95% CI [-0.44, -0.03], p= 0.03). Emotional eating was not significantly associated with age (β= 0.04, 95% CI [-0.02, 0.11], p= 0.18), BMI (β= -0.12, 95% CI [-0.27, 0.03], p= 0.12), depression level from the HADS (β= 0.1, 95% CI [-0.29, 0.5], p= 0.61). Higher scores in emotional eating was significantly associated with male gender.

The detailed findings of the relationship analyses are demonstrated in Appendix 8.

3.4. Discussion

3.4.1. Synthesising the key findings

- Depression and anxiety in the current study population

In the current study, our participants were moderately anxious and depressed which concurs with previous studies in newly-diagnosed OSA populations (192, 308). However, we did not find any strong association between OSA severity and levels of anxiety and depression.

Given that 20% of the participants in this study reported the consumption of anti-depressants, it may be possible that the overall anxiety and depression level reported in this group was moderated due to taking antidepressant by some of the participants. Furthermore, our participants were diagnosed with OSA shortly before they had been referred to our study. As such, their self-reported level of perceived anxiety and depression (assessed by the BDI-II and

HADS questionnaires) may have been influenced by being newly diagnosed with OSA and being informed that they needed CPAP treatment. Such emotional/psychological impact of being diagnosed with OSA could not be eliminated from the overall anxiety and depression levels, which have been measured at this initial timepoint. Taken together, with any alteration in the factors stated above, we could have possibly found a different proportion of participants with anxiety and depressive symptoms in the current study. A greater level of anxiety and depression could have possibly resulted in uncovering stronger significant relationships between anxiety/depression levels and other variables (e.g., OSA severity and eating behaviour) in our study.

- The relationship between AHI and BMI

Results from the current study showed that AHI is significantly associated with BMI. This finding was in accordance with previous studies which suggested the existence of an association between AHI and BMI, either in patients with OSA in general (73, 314-316) or exclusively in newly-diagnosed patients with OSA (192, 308). Not surprisingly, this finding adds to the evidence from previous studies reporting the relationship between OSA severity and obesity. However, the weakness of the relationship between OSA severity and BMI in the current study (r^2=0.109) suggests the existence of other factors which are likely to play a role in OSA pathogenesis, regardless of the level of AHI.

The current state of knowledge suggests that individuals with the same level of obesity are likely to present varied levels of OSA severity. Since OSA is a multifactorial disorder, an interaction of several physiological traits have been demonstrated to result in differences between individuals regardless of presenting the same level of AHI. A wide range of anatomical (e.g., inadequate upper airway muscle function, high loop gain) and non-anatomical (e.g., over-sensitive ventilator control system, low respiratory arousal threshold) features are suggested to contribute to the development of OSA and its symptoms (272, 317). The presence/absence of such traits in our participants may have affected the relationship between OSA and its well-known accompanying condition; obesity.

- Correlation between depression scores from the HADS and the BDI-II questionnaire

When designing the trial, there was limited evidence as to which depression screening tool (the BDI-II OR the HADS questionnaire) was optimal to use in patients with OSA. Not surprisingly, using the BDI-II and the HADS questionnaire in the current study resulted in finding (1) a significant positive correlation between the depression scores from the BDI-II and the HADS questionnaire, and (2) a similar non-significant association between depression symptoms and other studied variables (i.e., OSA severity, eating behaviour, age, gender, and BMI). Such findings suggest that these two questionnaires may be similar in detecting depression levels in a population with OSA.

Interestingly, we found a large variability in the scatter plot of the BDI-II and the HADS questionnaire (Figure 15), in which only a small proportion of this variability (r^2<0.15) could be explained by the relationship between the BDI-II and the HADS questionnaire. The large variability found in this study may possibly be explained by the structural differences in the two questionnaires, including (a) the time period that the BDI-II and the HADS questionnaire is designed to assess: a two week versus one week time period for the BDI-II and the HADS questionnaire, respectively; and (b) the type of aspects/feelings that these two questionnaires measure: the BDI-II questionnaire measures depression levels through questions regarding hopelessness, irritability, guilt or feelings of being punished and physical symptoms (e.g., fatigue, changes in appetite, and lack of interest in sex), while, the HADS questionnaire evaluates levels of depression in those with physical ill-health through focusing on non-physical depressive symptoms without considering factors such as appetite, sleep and self-harm/suicidal thoughts (184).

- Relationships between OSA severity (as assessed by the AHI) and (a) BMI, (b) three aspects of eating behaviour, (c) anxiety and depression

The current study was the first to assess the relationship between OSA severity (assessed using the AHI) and eating behaviour. Our findings suggested that OSA severity and eating behaviour (i.e., cognitive restraint, uncontrolled eating, and emotional eating) are not related. Moreover, we found a lack of association between OSA severity and levels of anxiety and depression symptoms. This finding was in line with the results of the previous studies (192, 308) that could not find a relationship between AHI and levels of anxiety and depression symptoms (using the BAI and the BDI-II questionnaire). Given that we could not detect any association between AHI and eating behaviour in the current study, there may be some underlying factors attributing to weight gain which (a) could not be accurately measured with the TFEQ-R18 questionnaire, and/or (b) have not been taken into consideration in the TFEQ-R18 questionnaire. Moreover, there might be factors other than AHI levels (respiratory events and arousal frequency) in OSA patients that are related to eating behaviour in this population.

- Associations between demographic variables and eating behaviours (i.e., gender, age, BMI, cognitive restraint, uncontrolled eating, and emotional eating), with the levels of anxiety and depression

In the present study, we did not find any association between gender and levels of anxiety and depression. Our findings are contrary with previous studies in OSA population which have reported that women tend to be more anxious and depressed than men (189, 318-320). The lack of association between gender and anxiety/depression in the current study may be partly explained by (a) the small proportion of recruited women (27%) than men (73%); and (b) the greater number of women (43.8%) under treatment with antidepressants compared to men (11.4%). Our analyses also did not find any relationship between age and levels of anxiety and depression. This result was in agreement with a previous study in newly-diagnosed OSA

population which reported the lack of association between age and levels of anxiety and depression (192). Furthermore, no association was found between BMI and levels of anxiety and depression in the current population. This finding was in agreement with the results of a previous study in patients newly-diagnosed with OSA, which revealed no correlation of obesity either with anxiety (using the BAI) or with depression (using the BDI-II) (192).

The current study was the first to investigate the relationship between eating behaviour and levels of anxiety and depression in OSA population. In contrary to our hypothesis, none of the three aspects of eating behaviour were related to the levels of anxiety and depression in our OSA population. However, in a previous study in Swedish, middle-aged men and women with obesity and without OSA, anxiety and depression levels (using the HADS questionnaire) were found to be associated with emotional eating, but not with the other two aspects of eating behaviour (i.e., cognitive restraint, and uncontrolled eating) (312). Such results suggest that in OSA patients, other factors than only the levels of anxiety and depression play a role in presenting different patterns of eating behaviour.

- Associations between demographic variables (i.e., gender, age, BMI), and three aspects of eating behaviours (i.e., cognitive restraint, uncontrolled eating, emotional eating)

Among three aspects of eating behaviour, only emotional eating was significantly associated with male gender., A previous study suggested that in a non-OSA population (54% women versus 46% men) with obesity, emotional eating is higher in women compared to men (312, 321). Moreover, in a population of non-OSA primary care patients (69% women versus 31% men) with obesity, women were found to have greater scores in emotional and uncontrolled eating (using the TFEQ-R18 questionnaire) (322). Interestingly, in both of the previous studies (312, 321, 322), the proportion of women was greater compared to men. In opposition to both previous studies, majority of the participants in the current study were consist of men. Accordingly, a) an inverse proportion of women and men; and b) a small proportion of women (27%) compared to men (73%) in the current OSA population may have attributed to the discrepant relationships found between eating behaviour and different genders reported in the current versus previous studies (312, 321, 322).

Further, we did not find any relationship between age and any of the three aspects of eating behaviour. However, we found BMI to be negatively associated with uncontrolled eating in our population, which was in contrary to the results of a similar study in non-OSA population which reported BMI to be associated with the three aspects of eating behaviour (156, 323). The discrepancies in our findings compared to previous evidence (156, 323) may be partly explained by including participants with a wider range of BMI (15.72–55.36 kg/m^2) whom were not necessarily obese, compared to our inclusion of overweight and obese individuals (BMI range: 23–43 kg/m^2). However, no previous evidence of investigating such associations could be found in OSA population in order to be used for a more accurate comparison.

3.4.2. Strengths and limitations

The strengths of our study were: a) given the objective measurement of AHI and BMI based on the guidelines, the risk of any biased measurement and misclassification in the current study should have been avoided; b) we assessed the association of eating behaviour with OSA severity which have not been previously explored in a sample population of patients with OSA; c) our exclusion of patients with mild OSA may be seen as a limitation, when looking at first glance. However, the decision for including those with moderate-severe OSA was based on the evidence that patients with higher OSA severity are more likely to have greater levels of obesity (308, 314-316). Thus, those with more severe OSA could benefit best from weight loss when aiming to manage their OSA severity; d) to the best of our knowledge, this is the first study investigating eating behaviour and its relationship with OSA severity and anxiety/depression in newly-diagnosed patients with OSA; and e) excluding participants with major health issues (e.g., diabetes mellitus type 2, severe psychiatric disorders, and concomitant obesity hypoventilation syndrome) was conducted with an aim to attenuate the risk of other comorbidities influencing the studied associations.

Nonetheless, the present study has several limitations to consider: a) the relatively small sample size which may be an underlying factor for lack of statistical significance in majority of our studied associations; b) Using subjective self-rating scales (the HADS, BDI-II, and TFEQ-R18 questionnaires) may have increased the risk of exaggeration or under-reporting of the studied variables. However, so far, there has not been a better alternative for measuring such variables to be implemented in this study; c) The association between gender and other studied variables in the current evidence may have been potentially influenced by unequal distribution of sex ratio in our population (73% men vs. 27% women). However, due to the greater prevalence of OSA among men compared to women, the proportion of recruited men and women in the current study represents an expected sex ratio in the OSA population; d) considering the interaction that has been suggested between obesity and anxiety/depression (192, 206, 324, 325), limiting our inclusion to patients with overweight and obesity may have influenced our results; e) the results of this study cannot be generalised to the general population with OSA as we have excluded patients with specific characteristics based on our inclusion criteria (see Table 9). However, excluding those with major comorbidities was assigned aiming to eliminate the potential role of other comorbidities in our studied associations.

3.4.3. Final remarks

The current study included a population of adults newly-diagnosed with moderate-severe OSA who were recruited from public hospitals in Victoria, Australia. The included population were mild-moderately depressed, even though some of them were treated with anti-depressants on enrolment into the trial.

A significant correlation was observed between depression scores generated from the HADS and BDI-II questionnaires in the current study. Moreover, a significant relationship was noted between AHI and BMI in the current population. However, AHI was linked neither to eating behaviour, nor to the levels of anxiety and depression. No relationship could be seen between eating behaviour and levels of anxiety and depression, either. Age showed no relationship between eating behaviour and levels of anxiety and depression. Except for emotional eating, gender difference did not show any association with either cognitive restraint or uncontrolled eating or anxiety and depression levels. Further analyses showed a lack of association between BMI and levels of anxiety and depression. Although, a significant association was observed between BMI and uncontrolled eating, neither cognitive restraint nor emotional eating were found to be related to BMI in this population.

Except for the significant relationship between BMI and AHI which has been repeatedly reported in newly-diagnosed patients with OSA (192, 308), no strong relationships could be detected between other variables (i.e., age, gender, eating behaviour, and levels of anxiety and depression) that have been studied in the current evidence. Similar to the previous evidence (192, 308), the few significant relationships observed in this study were mainly weak. The lack of strong associations in our findings suggests that there might be different underlying factors attributing to the anxiety and depression levels, eating behaviour, and disease severity in patients with OSA which could not have been detected with any of the measurement tools that have been employed in this study. This suggests that severity of OSA should not be assumed to relate directly either to eating behaviour, or anxiety and depression levels.

Based on these findings, future studies could focus on recruiting a larger number of patients to determine whether our non-significant findings are consistent in this group of patients who were recruited from two large public hospitals. Future research should also be conducted utilising different measurement tools and questionnaires that have not been used in this study in order to explore whether there are other factors that have linked OSA and obesity (e.g., food intake and hormonal status) in patients newly-diagnosed with OSA. Better understanding of the factors linking OSA and obesity may help healthcare professionals to provide a more effective treatment regime and weight loss advice, once an individual is diagnosed with OSA.

Chapter 4: Discussion and conclusion

4.1. The research findings

This thesis contributes to the knowledge about a) the effectiveness of the lifestyle interventions (diet, exercise or a combination of the two) in reducing OSA severity; and b) the relationships between OSA severity, eating behaviour and anxiety/depression levels in a population of adults newly-diagnosed with OSA.

In chapter 2, we conducted a systematic review and meta-analysis of 12 RCTs to reveal the most effective type of lifestyle interventions (diet, exercise, or combination of the two) in reducing OSA severity and BMI. Our results suggest that diet-based interventions (with a focus on decreasing calorie intake) when used either alone or in combination with exercise, have the best outcome in terms of reducing both an individual's OSA severity and obesity levels. Adding exercise to diet-based interventions may provide additional health improvements for obese individuals. However, exercise-based interventions were not found to be as effective as diet-only or combined interventions in reducing level of OSA severity and obesity. We concluded that diet-based interventions are the most effective type of lifestyle intervention for reducing OSA severity and should be considered as an essential component of any lifestyle intervention therapy for patients with OSA. Importantly, neither baseline BMI, AHI, nor the length of the intervention were observed to be associated with changes in AHI or BMI following the interventions.

Considering that the majority of OSA patients are obese and they may substantially reduce their OSA severity by losing weight (as suggested by the results from our systematic review and meta-analysis), we also chose to explore in more details potential underlying factors that may have induced obesity in patients with OSA. Thus, we conducted a cross-sectional analysis of the baseline data collected from an RCT (Chapter 3), to investigate the associations between OSA severity, eating behaviour and levels of anxiety and depression. Our study population comprising adults newly-diagnosed with moderate and severe OSA were found to have moderate levels of anxiety and depression. Those with severe OSA were more likely to have higher BMI levels, as per previous studies (314-316). However, we did not find strong relationships between OSA severity and any of the three aspects of eating behaviour (i.e., cognitive restraint, uncontrolled eating, and emotional eating) and levels of anxiety and depression in the current study population. The lack of strength in the studied association suggests the existence of other factors not captured by eating behaviour questionnaires that are likely to play a role in the development of OSA and its well-known accompanying conditions (e.g., obesity, anxiety, and depression).

We also found that depression scores from the HADS and the BDI-II questionnaires positively, but weakly correlated ($P<0.01$, $r=0.36$). Accordingly, using either the HADS or the BDI-II

questionnaires for measuring depression levels is expected to result in similar findings when exploring the relationship between depression and other variables in the current study.

Based on the current knowledge, there is a well-known association between BMI and AHI. However, lack of strength in the relationship between BMI and OSA severity in our findings suggests the existence of other mechanisms/factors (e.g., actual eating behaviour, hormonal status) that may potentially link BMI and OSA severity. Moreover, lack of association between many of the studied variables suggests the potential role of other factors related to eating behaviour, anxiety/depression, and disease severity in patients with OSA. It may also be argued that the absence of strong associations in the current study is due to the existence of factors other than AHI levels (respiratory events and arousal frequency) in OSA population. However, such factors or mechanisms could not be detected in our study population with using the measurement tools that we utilised. We conclude that except for the BMI which showed to be associated with AHI levels, OSA severity (assessed by using AHI levels) should not be assumed to directly relate to eating behaviour or/and anxiety and depression levels.

4.2. Clinical recommendations

The increasing rate of obesity in the world is expected to dramatically elevate the incidence rate of OSA in the coming years. Thus, one of the important priorities for healthcare professionals will be to determine the most effective ways to manage the treatment of OSA. To pursue this aim, it is crucial to firstly explore the most effective treatments available, and secondly, to understand the underlying factors and mechanisms that link OSA and obesity. Discovering complex interactions between OSA and weight gain may assist in establishing more targeted strategies to better manage the treatment of this complex disorder.

Identifying the most effective type of lifestyle intervention (diet, exercise, or combination of the two) for the management of OSA is a crucial step for healthcare professionals who introduce treatment strategies to OSA patients. The findings of the systematic review and meta-analysis (chapter 2), revealed that the greatest beneficial effects for the management of OSA severity is achieved using diet-based interventions (reduced-calorie diets) compared to exercise-based interventions alone, or combined (exercise and diet) interventions. Importantly, results from our systemic review demonstrated that increasing exercise may confer health benefits, although they would not be expected to improve OSA over and above achievements from dietary changes alone.

Nevertheless, to help healthcare professionals to a) obtain a good understanding of the underlying factors that may have tied OSA and obesity, and b) establish targeted treatment strategies for newly-diagnosed OSA patients, relationships between OSA severity and factors including BMI, eating behaviour, and levels of anxiety and depression have been investigated in the current thesis.

Not surprisingly, our study population (chapter 3) comprising newly-diagnosed moderate-severe OSA patients were moderately anxious and depressed. Although OSA severity found to be associated with BMI, but none of the factors including eating behaviour and levels of anxiety and depression could adequately explain such relationships.

Findings from the current study population (chapter 3) showed that neither eating behaviour, nor levels of anxiety and depression should be assumed to be directly related to the severity of OSA. It is of importance to note that the presented results are limited to newly-diagnosed, untreated OSA patients with AHI≥20 events/hr, and BMI less than 43 kg/m^2, with no reports of having major comorbid illness (as per our inclusion criteria) (Table 9). Thus, altered patterns may be reported in different OSA populations and our findings may not be generalised to entire OSA population, in particular to those with mild OSA.

4.3. Future directions

Considering that the relationship between OSA and obesity exists, it is important to find an effective strategy to tackle obesity in OSA patients. Therefore, there is a need for further studies attempting to a) clarify the potential factors inducing weight gain in OSA patients; and b) establish appropriate treatment strategies that consider the pathway(s) linking OSA and obesity.

To pursue this aim, it is essential for future systematic literature review studies to include a greater number of RCTs and possibly more number of exercise-based intervention studies. In addition, further RCTs are required to explore how the timing of an intervention would affect weight and AHI. Another question that remains unanswered is whether the type or duration of an intervention may alter outcomes for patients with OSA. Reviews including such RCTs may reveal whether our findings are robust or there is a need for alternations in diet or exercise component of the lifestyle interventions in order to optimise OSA treatment. In addition, given the relatively little number of good long-term follow-up studies performed, a greater number of long-term (i.e. greater than a minimum of one year) follow-up studies will likely be needed to reveal the long-term benefits of different types of lifestyle interventions in reducing obesity and disease severity levels in OSA patients. Given that the current study could not accurately pinpoint the mechanisms/factors responsible for the well-known relationship between OSA and obesity, there is a great need for a) further evidence to elucidate pathways that link OSA and obesity; as well as b) comprehensive physiological studies to illuminate the stream in which obesity leads to forming/worsening of OSA.

It would be worthwhile to conduct further randomised controlled trials, similar to the current study, however, with using a) a larger sample size, b) different measurement tools and questionnaires, c) different type of intervention, and d) different intervention

commencement date and duration, to confirm whether our findings are robust/repeatable. Moreover, it will also be helpful in future work to consider assessing whether the existence of other potential factors (e.g., actual food intake, hormonal status) may better explain the relationship between OSA and obesity. Such findings may provide greater evidence to explain mechanisms by which OSA and its severity relate to overweight and obesity. Nevertheless, a more comprehensive understanding of the factors linking OSA and obesity may help healthcare professionals to establish robust and evidence-based strategies to better assist OSA patients to manage their weight and OSA severity.

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Appendices:

Appendix 1: Databases and search terms used for conducting the systematic review and meta-analysis

Database	Search terms
CINAHL	sleep*, diet*, food*, eating*, beverage*, nutrition*, exercis*, physical* activ*, fitness*, sport*, sleep apnoea, obstructive
Cochrane	sleep*, diet*, food*, eating*, beverage*, nutrition*, exercis*, physical* activ*, fitness*, sport*, sleep apnoea, obstructive
Embase	sleep*, diet*, food*, eating*, beverage*, nutrition*, exercis*, physical* activ*, fitness*, sport*, sleep apnoea, sleep apnea
OVID Medline	sleep*, diet*, food*, eating*, beverage*, nutrition*, exercis*, physical* activ*, fitness*, sport*, sleep apnoea, obstructive
Scopus	sleep*, diet*, food*, eating*, beverage*, nutrition*, exercis*, physical* activ*, fitness*, sport*, sleep apnea, obstructive sleep apnea

Appendix 2: Study protocol for the Sleeping Well Trial (version 11), Date of the latest amendment's approval: 16/10/2017

MONASH University

STUDY TITLE:

The Sleeping Well Trial: enhancing the effectiveness of continuous positive airway pressure (CPAP) treatment with a weight management program for overweight adults

Principal Investigator:	Professor Helen Truby	
Co-Investigators:	Dr Bradley Edwards	Assoc Prof Garun Hamilton
	Dr Maxine Bonham	Prof Terry Haines
	Dr Alan Young	Prof Matthew Naughton
	Dr Denise O'Driscoll	Dr Simon Joosten
	Ms Teanau Roebuck	Dr Chiara Murgia
	Miss Kellie Hamill	Mrs Kerryn Roem
	Miss Claire Bristow	
Student researchers:	Ms Ladan Ghazi	Ms Kirsty Yull
	Ms Kaitlin Day	

Trial registration ID: ACTRN12616000203459

INTRODUCTION:

Obstructive sleep apnoea (OSA) is a highly prevalent disorder with serious cardiovascular and neurocognitive consequences (326). Importantly obesity, which is the strongest risk factor for OSA, is a growing epidemic and is one the western world's leading health care concerns (327). Interestingly, recent evidence suggests that OSA and obesity share a bi-directional relationship. It has clearly been established that obesity contributes to the development of OSA by promoting upper airway collapse. However, the reciprocal relationship has not been critically examined. It has been proposed that sleep fragmentation associated with OSA, contributes to the development of obesity, by altering energy balance. Sleep fragmentation promotes energy intake (328) by increasing the production of orexigenic hormones, and decreasing physical activity due to its association with excessive daytime sleepiness. Particularly, OSA itself can reinforce the obese state via alterations to energy metabolism, appetite and satiety via neural control feedback mechanisms, thereby making it harder for those with OSA to manage their weight and also maintain weight loss (130).

Currently continuous positive airway pressure (CPAP) is considered the gold standard treatment as it improves symptoms and reduces cardiovascular mortality (329). Unfortunately, previous studies suggest that CPAP may accelerate the pace of weight gain in patients with OSA (257), which is driven by in body composition (lean and fat mass) (330, 331). As these studies implemented different study designs and durations, it makes it difficult to compare the conflicting results and demonstrate a significant pattern. Interestingly, other studies suggest that physical activity and/or dietary intake do not change by following CPAP treatment (332, 333). Consequently, changes in body composition in CPAP users are more likely to be explained by mechanisms directly related to alleviation of OSA, than any changes in physical activity or dietary intake (333). Regardless of these findings, it is still controversial what is the origin of weight gain in CPAP users, but what is clear is that using CPAP may increase body weight which is itself an independent risk factor for OSA (257) and any treatment that increases weight gain is undesirable for CVD risk and risk of developing Type 2 diabetes.

Considering the weight gain followed by CPAP treatment, weight loss interventions need to be used as a parallel strategy in patients with OSA. To improve weight loss, lifestyle interventions (e.g., diet and/or exercise) are common recommendations. Not surprisingly, studies that have combined interventions involving both diet and physical activity have shown to be successful in obtaining the most effective results in reducing OSA severity (270, 274). The study by Papandreou *et al.* (2012) employed a combination of diet and physical activity intervention in obese CPAP users for a short duration of 12 weeks which demonstrated a large decrease in apnoea hypopnoea index (AHI) in the interventional group compared to control group (-15.6 events/hour versus -14 events/h). Interestingly, in another randomised controlled trial by Kemppainen et al. (2008), applying a combination of diet and physical activity intervention resulted in a significant reduction in body mass index (BMI) in the intervention group than that achieved by patients in the control group (5.4 kg/m2 versus 0.5 kg/m2). Despite the promising effects that lifestyle interventions have been shown to have on both OSA severity and body weight, there are a number of limitations in these studies:

- To our knowledge, none of these studies have investigated if more effective results in weight or OSA severity could be achieved by changing the initiation of a lifestyle intervention for CPAP users, nor has there been any investigation into whether the changes in body composition follow different patterns by time following CPAP treatment.
- Most of the studies in OSA patients have focused on patients with mild-moderate disease severity. Thus there is a need to understand if different treatments (or strategies) could be used more effectively in moderate-severe OSA patients, as this encompasses the majority of the disease burden.
- Again, most of the current studies are observational or short-term randomised controlled trials (conducted in less than 12 months).
- Lastly, successful long-term behaviour modification requires building motivation and regular support (334) which is worthwhile in interventional studies. Accordingly, there is a need for developing a strategy for proper, regular support, if there is no other way than face-to-face visits.

Even though a few studies have concluded that changes in body composition occur during CPAP treatment, due to differences in study designs and periods, it is not possible to compare their findings to find out at what point in time these changes in body composition happen. Therefore, it is important to employ a study design that let us monitor changes in body composition at different relative time-points, among individuals who share the same characteristics and are treated the same. However, it is still unclear when these changes start to manifest during CPAP treatment period, and when is the best time to start managing their weight gain.

We are interested in investigating how body composition in individuals who undergo CPAP treatment changes over time, and to identify when the best time to introduce lifestyle intervention to this group is. In this trial we will monitor the effectiveness of a variable commencement time of the lifestyle intervention in participants diagnosed with moderate-severe OSA, who are already established on CPAP therapy. In particular, we will introduce dietary and physical activity intervention alongside utilising myPace application to provide between-visit support for individuals to enhance their compliance with lifestyle intervention instructions. We hope that such a finding will extend our knowledge of effective treatment pathways that are applicable in practice settings. The result of this trial is expected to reveal if there is any ideal time for introducing lifestyle intervention for CPAP users to maximise their outcome in weight loss and severity of OSA.

There are two primary research aims. 1) To investigate the effectiveness of the lifestyle intervention for reducing weight gain experienced by people with OSA commencing CPAP. 2) To investigate whether timing of commencement of lifestyle intervention affects the change in weight experienced by these people.

STUDY PROTOCOL

Design:

Randomised controlled trial utilizing 6 different delay periods between commencement of CPAP and commencement of the lifestyle intervention. There will be groups with 1, 2, 3, 4, 5, and 6 months delay. Thus this randomised controlled trial will take the appearance of a stepped-wedge, waiting list design. However, unlike conventional stepped-wedge designs, this trial will not involve cluster randomisation. It will instead utilise randomisation of individual participants.

Participants:

Participants who are overweight (Asian and Indian heritage participants with a BMI from 23 to 43 kg/m^2 and other heritage BMI range 25 to 43 kg/m^2), have been recently diagnosed with moderate-severe OSA and recommended treatment with CPAP will be identified from two sleep centres in Melbourne; Monash Medical Centre (Assoc Prof Garun Hamilton and Dr Simon Joosten), and Box Hill hospital (Dr Alan Young). The Alfred Hospital site may be included if recruitment is problematic in the other sites. In each centre, the identified individuals will be introduced to the study and if they are interested, will be screened if they

are currently pregnant, have been diagnosed with Diabetes Mellitus, severe psychiatric disorder, and drowsiness. Individuals who are eligible will be asked by their sleep physician to provide verbal consent for performing further contact about the study. After finishing appointment with sleep physician, potential participants will be contacted by a student researcher via phone. They will be briefly informed about the study procedure and asked if they are still interested to participate in the study. All potential participants will be briefly questioned about their medical history in order to confirm that they meet inclusion criteria (see below).

Inclusion criteria:

- Adults aged 19-68 years
- Moderate-severe untreated OSA with AHI≥ 20 events/hr (AASM alternate criteria) (demonstrated by prior overnight polysomnography [PSG])
- Participants who are overweight (Asian and Indian heritage participants with a BMI from 23 to 43 kg/m^2 and other heritage BMI range 25 to 43 kg/m^2),
- Sedentary (self-reported exercise < 2 days/week and ≤ 45 minutes per session)
- Required and eligible to use Fixed-Pressure Continuous Positive Airway Pressure *(*CPAP*)*

Exclusion criteria:

- Pregnant women
- Diagnosed with concomitant obesity hypoventilation syndrome, Diabetes mellitus type 1 or 2 (if on insulin treatment), severe psychiatric disorder, and drowsiness
- Commercial drivers
- Required to use "VPAP" or "BPAP" (*variable*/bilevel positive airway *pressure*)
- Unable to exercise (e.g. due to orthopedic or musculoskeletal problems)
- Previous surgical or current medical treatment for OSA
- Previous bariatric surgery
- Current use of weight loss programs and/or weight loss drugs
- Recent angina pectoris or atrial fibrillation
- Allergic to cow's milk protein
- Insufficient knowledge of English language
- Unable to provide informed consent

Potential participants will be invited for a screening session ~60-90 minutes starting between 8 and 10 am, at Be Active Sleep & Eat (BASE) facility in Notting Hill. They will be asked to fast overnight (for 10-12 hours) before coming to the session. After providing written consent, they will be enrolled into the study. They will be required to provide their personal information in the provided participant's data collection sheet. Their weight will be assessed by using a calibrated digital scale by Seca. Subsequently, their blood pressure, height, waist and neck circumference will be measured. A qualified phlebotomist will ask for a verbal consent and obtain a 17 ml blood sample from each participant. Blood samples will be frozen immediately in the biohazard freezer at BASE facility. After blood collection, a light breakfast

(cereal, fruit, milk, coffee or tea) will be provided for participants. Ultimately, they will be asked to complete questionnaires about Functional Outcomes of Sleep (FOSQ), Epworth Sleepiness Scale (ESS), eating behaviour (TFEQ-R18), health-related quality of life (EQ-5D), activity level (IPAQ-SF), general health status (SF-36), and history of depression (BDI), and anxiety status (HADS). On participants' final appointment, they will be asked to complete a feedback form including questions of intention to continue treatments provided in the trial, as well as general comments and/or suggestions about their study experience.

Group allocation:

We are aiming to recruit of total of 60 into this study. At this point, every participant will be individually randomised into 1 of 6 intervention groups by implementing allocation concealment by the study statistician; groups 1-6 correspond to when the lifestyle intervention will be introduced after initial commencement of CPAP therapy (Fig. 1). For example, group 1 will start their lifestyle intervention one month after starting CPAP therapy. Once the lifestyle intervention has commenced, it will last for 6 months. Outcomes of this study reveal if the lifestyle intervention will be effective in changing weight trajectory experienced by people with OSA who are undergoing CPAP therapy. It will also determine if outcomes of intervention would be different in different groups who started and finished their intervention at different timepoints.

At this stage, every participant will be offered a Fitbit Flex wireless activity and sleep tracker wristband for free. Instructions on how to use their Fitbit tracker will be provided and all participants will be asked to use their Fitbit during 12 months of the study. Each participant will be asked to sign a receipt after receiving their Fitbit tracker. A personal online account will be created in Fitbit website for each participant. Based on the written consent form, obtained at recruiting time, researchers will have permission to access participants' personal online account to monitor their activity information. Participants are allowed to keep their tracker after finishing the study.
After all, an appointment will be organised for each participant to visit one of the three Air Liquide CPAP clinics (located in Richmond, Dandenong and Eltham). A referral letter will be provided for each participant to visit CPAP clinics and receive their CPAP machine. CPAP consultants will assist participants with instructions to commence CPAP therapy.
At the end of this session, every participant will be provided with a document folder to take home. This folder contains a fact sheet about OSA, a list of general tips for sleeping well, a copy of their signed information sheet and consent form, and a flow chart that helps them to easily understand their pathway during 12 months of this study.

CPAP management:

CPAP implementation will be provided for all patients by Air Liquide Healthcare. During the first visit to Air Liquide CPAP clinics, patients will undergo mask fitting and education regarding sleep apnoea and CPAP use by staff at Air Liquide. Patients will initially be commenced on Autotitrating CPAP using a Resmed S9 CPAP machine. After 1 week of treatment, patients will be switched to fixed pressure CPAP based on the 95th centile

pressure determined during the autotitration week. Routine equipment troubleshooting will be provided by Air Liquide, in conjunction with the patient's treating physician. Patients will undergo routine CPAP care co-ordinated by their physician. All decisions regarding any treatment changes will be made by the treating physician. Participants are required to use their CPAP devices regularly for 12 months period (beginning from consent date). Overall, during 12 months of CPAP therapy, each participant will be provided with 5 face to face consultation sessions (at time of set up, day 7, 1 month, 6 month, and 12 month), and 2 follow up calls (day 3, and day 21 following the time of set up) arranged by Air Liquide. During each consultation session, participants will be asked to provide their CPAP machine and allow CPAP clinicians to extract its data. The extracted data will be uploaded in each patient's personal account in My Vitality Club Pro which is a website developed by Air Liquide Healthcare and gives researchers and sleep physicians the possibility to access patient's clinical data and monitor their progress with CPAP therapy. The data extracted from CPAP machines will be accessible by both sleep physicians and researchers in this study. During each visit to Air Liquide CPAP clinics, participants will also be asked to undergo weight measurement by using a calibrated digital scale. The weight records will be reported to the study coordinator, while sleep physicians will be kept blinded to this information.

Lifestyle intervention:

The time that each participant is invited to undergo the lifestyle intervention, depends on the group that they are allocated to. The waiting time before undergoing lifestyle intervention can vary between 1-6 month(s) after CPAP treatment is initiated (Fig. 2).

During the introductory session to lifestyle intervention, participants will need to undergo weight measurement using a calibrated digital scale by Seca, followed by blood pressure and body measurement (i.e. waist and neck measurement). A qualified phlebotomist will obtain 17 ml blood sample from each participant which will be frozen immediately in the biohazard freezer at Base facility. Pre- and post-intervention blood samples will then be delivered to Monash University laboratory for gene expression analysis. Participants will be asked to provide a written consent for undergoing Dual-energy X-ray absorptiometry (iDXA) scan. Body composition will be measured with the iDXA machine which will be operated by a qualified radiographer. For this purpose, participants will need to lie on a padded table for approximately 10 minutes while the scan is performed. For this study we will perform two iDXA scans at two different timepoints and once the scan is completed, a copy of iDXA scan will be provided for study dietitian. Participants may also ask for a copy of their iDXA scan to keep it for their own records. After iDXA scan, a light breakfast (cereal, fruit, milk, coffee or tea) will be provided for participants. Ultimately, participants will be asked to complete questionnaires about Functional Outcomes of Sleep (FOSQ), Epworth Sleepiness Scale (ESS), eating behaviour (TFEQ-R18), health-related quality of life (EQ-5D), activity level (IPAQ-SF), general health status (SF-36), and history of depression (BDI), and anxiety status (HADS).

After completion of the assessment, every participant will have a 60 minute counselling session with an accredited practising dietitian (APD) at BASE facility. The dietitian will explain about 6 months of the lifestyle intervention which involves an active weight loss phase (initial 3

months) and maintenance phase (the second 3 months). The active weight loss phase includes diet and exercise. The diet comprises a combination of an intermittent fasting diet and a reduced energy diet. Participants will be asked to try and adhere to this diet throughout the initial 3 months of the lifestyle intervention. They will be encouraged to schedule at least three 30 minute sessions of light physical activity (e.g. walking or jogging) each week during the active weight loss phase; however monthly visits with dietitian will continue for a total of 6 months of the lifestyle intervention. In the first visit with dietitian, participants will be asked to install the myPace application on their smartphone or tablet device to use in between consultations with dietitian. MyPace has been developed to promote weight management and permit communication with the dietitian. The instructions on how to use the application will be provided by the dietitian. Participants who do not have access to smartphone or tablet device, will receive regular phone calls from dietitian to provide an effective communication pathway with participants.

Once participants are introduced to lifestyle intervention, they are required to follow a low energy diet and exercise recommendations for initial 3 months and also attend 6 monthly visits with dietitian.

A Fitbit tracker which had been provided for participants to use at the time of recruitment, will record each participant's activity history which will be stored in each participant's personal online account. Fitbit participant's accounts will be accessible by the researchers during 12 months of the study. Besides, study dietitian will have permission to access this information during 6 months of the lifestyle intervention. The recorded daily activity helps dietitian to assess participants' compliance with physical activity recommendations.

The low energy diet consists of five days of restricted daily energy intake using reduced-fat/low-fat diet of 6300-7500 kilojoules (kJ) per day and two days of very low energy intake which provides between 2200-2760 kJ per day. For days with structured low energy intake, participants will be provided with nutrition pack which will last for a month. The nutrition pack consists of proportioned skim milk powder, multivitamins with fish oil and fibre supplements. During the active weight loss phase (initial 3 months of lifestyle intervention), nutrition packs will be provided every month, until the next visit with dietitian. Participants will be asked to mix the skim milk powder with skim milk/reduced fat milk at home. For each day that participants consume the structured low energy intake, they will be asked to use the skim milk powder with milk, multivitamin, and fish oil and fibre supplements for two meals and for the third meal they will be asked to eat a low energy frozen meal (suitable options will be discussed by the dietitian).

Dietitians will help participants with extra support between monthly consultations by using myPace application or regular text messages and phone calls. Participants will also receive individualised 'small steps' through the app which are simple action-based goals (e.g. eating, behaviour and physical activity oriented) that helps them with their weight management goals.

The initial and final (6th) visit with dietitian will be located in BASE facility and arranged by study researchers. At initial visit and one month after the last visit with the dietitian,

participants will be asked to complete the same questionnaires, provide a 17 ml of their blood sample, and also undergo iDXA scan (following the same procedure) for assessing changes in their body composition. The first appointment with the dietitian will last 60 minutes, however other monthly visits last 30 minutes and can be organised to be held either at BASE facility, or dietitian's rooms in North Fitzroy or Box Hill via the dietitian directly. At each visit the dietitian will record weight for each participant using calibrated digital scales provided through the study researchers.

Monthly visits:

As part of involvement in this study, participants are expected to let us measure weight every month (using a calibrated digital scale). Each visit for weight measurement may take ~5-10 minutes.

Options for weight measurement are as follows:

- At Air Liquide CPAP clinics (one month, 6 month, 12 month)
- At Box Hill Hospital, or Monash Medical Centre or Alfred Health sleep clinics
- At the dietitians rooms located in BASE facility, North Fitzroy or Box Hill
- If none of the venues above are suitable, a home visit may be arranged by one of the researchers.

If different weight measurements are recorded on slightly different dates but the same point in the protocol, the measurement made at the BASE facility will be taken as the weight at the timepoint (i.e screening, baseline or monthly weight).

Overnight sleep study:

All participants will need to come for a one-night sleep study after 12 months of CPAP therapy. They will be contacted one week prior to this session and asked to cease their CPAP treatment for one week. They may continue using CPAP after attending the overnight sleep study. They will then be scheduled to spend a night at sleep laboratory at either BASE facility or their referring hospital (i.e. Monash/Eastern Health). Participants will be asked to have their dinner before attending this session and arrive at BASE or referring hospital about 7:00 pm. To get prepared for sleep study, leads will be placed on their head and body for measurement of heart beat, blood pressure, muscle activity, eye movements, brain activity and oxygen level in the blood. Two stretchy belts around their stomach and chest will be used to monitor breathing and two sensors under the nose will measure the air flow. The lights will be turned off and the participant will go to sleep. Breathing and sleep will be recorded until approximately 6:00 am, when the participant will be woken up and all the study equipment will be removed. In morning, their weight will be measured using a calibrated digital scale by Seca. Subsequently, height, blood pressure, neck, and waist circumference will be measured. Participants who have been already fasted overnight will be asked for consent to provide 17 ml of their blood sample. It will let us examine changes in their gene expression and the levels of total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, glucose, insulin, leptin, cytokines, and adipokines compared to the beginning of the study. After blood collection, participants will need to complete questionnaires about

functional effects of daytime drowsiness on quality of life (FOSQ), daytime sleepiness (ESS), eating behavior (TFEQ-R18), health-related quality of life (EQ-5D), activity level (IPAQ-SF), general health status (SF-36), depression (BDI), and anxiety status (HADS).

At the end of this session, if conducted at BASE, a light breakfast (cereal, fruit, milk, coffee or tea) will be provided and every participant who successfully completed the study will be offered a discount letter to purchase a CPAP machine from Air Liquide and they will be able to keep the Fitbit tracker free of charge. If the overnight sleep study was conducted at referring hospital, participants will need to visit BASE for their final measurements and debriefing, shortly after their overnight sleep study appointment.

Follow-up study

After finishing the 12 months of the trial, researchers will ask participants if they are interested in participating in the follow-up study. If they successfully provide consent, they will be followed up for another year after completion of the initial one-year trial. During this phase of the trial, 2 follow-up assessments will be performed; the first one 12 months after completing the lifestyle intervention and the second one 2 years after initial enrolment (Fig. 2). During follow-up visits, weight will be measured using a calibrated digital scale. The questionnaires undertaken during the intervention period (as described above) will also be repeated and a single DXA scan provided.

This study will investigate the following primary and secondary outcomes through different assessment procedures within the initial first 12 months of the study and the following one year of the follow-up:

Primary outcomes:

- Weight (kg) (using a calibrated digital scale)
- Body composition (using iDXA scanner)

Secondary outcomes:

- Apnoea hypopnea index (AHI) (assessed during overnight sleep study)
- Compliance with CPAP therapy (hours of CPAP used recorded by CPAP device)
- Compliance with physical activity instruction (daily steps recorded by a Fitbit tracker)
- Body measurements (height, waist, and neck circumferences)
- Blood pressure
- Blood samples (total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, glucose, insulin, leptin, cytokines, adipokines, and changes in gene expression)
- Daytime sleepiness (ESS)
- Functional outcomes of sleep (FOSQ)
- Health-related quality of life (EQ-5D)
- Eating behaviour (TFEQ-R18)
- General health status (SF-36)
- History of depression (BDI)
- Anxiety status (HADS)

Study design:
We are going to implement the stepped wedge randomised controlled trial which is a research study design, gaining popularity in the evaluation of service delivery and quality improvement areas (259). It has certain advantages over standard randomised controlled trials which include enabling every participant to be exposed to the intervention and that the impact of time is assessed. This design consists of an initial period, where no clusters are exposed to the intervention. Eventually, at regular intervals (the “steps”) one cluster (one group) will be randomised to cross from the control to the intervention under evaluation (335).

In this study design we are interested to establish if the timing of delivery of a weight management intervention is important to overall weight changes after 12 months of CPAP therapy. Using a step wedge design, we account for the possible confounding effect of time by collecting data on weight at each month. The wedge element comes from the timing of the delivery of the intervention itself which is titrated to begin at either after 1, 2 3, 4, 5 or 6 months after starting CPAP therapy, individual participants will be randomised individually to one of the 6 wedges by the study statistician (Prof T Haines). Thus optimising the randomisation procedure but maintaining the advantages of the step wedge design. It is therefore imperative that each participant’s weight trajectory is recorded over the period prior to and during the intervention. Thus requiring each participant to be weighed and CPAP compliance recorded on a monthly basis.

Sample size calculations:
Our proposed research design has 6 separate “steps” (delay periods) not including the baseline assessment. If we were to recruit 7 participants into each group, it would provide 82% power to detect a main effect of the intervention of 1.5 Kg difference in weight between intervention and control assessments. This assumes a standard deviation of 3.09 Kg (based on previously collected local data), uses a conservative ICC of 0.01, and treats each individual participant as its own cluster (as this is the unit of randomisation). Collecting 10 participants per group will provide coverage within the trial for potential drop-outs and missing data while maintaining adequate trial power.

Statistical Analysis:
To address aim 1) primary outcome (weight) as measured during each month during the control and intervention periods of the stepped wedge design will be compared between periods. The main effect of the intervention will be examined using a multilevel, mixed effects, linear mixed model analysis approach. Fixed effects will be included in this model for “time” and “intervention”, while a random effect will be included for the effect of “participant”.

To address aim 2) we will examine the association between lifestyle intervention commencement month and weight at 12 month follow-up (adjusted for baseline weight). This analysis will treat "lifestyle intervention commencement month" as a continuous variable and examine both a linear and quadratic relationship with the outcome. We will examine whether there is a difference in the rate of change in primary outcomes between

control and intervention periods using a “time-by-intervention” interaction effect. Statistical adjustment will be made for other relevant variables in each of these analyses.

As a secondary exploratory analysis, we will aim to identify patients who are most likely to have their OSA resolved following weight-loss. In order to do this, we will identify two key physiological causes of OSA (the threshold for arousal and the sensitivity of the ventilatory control system) from the overnight PSGs as well as common clinical predictors that are significantly altered with weight loss. Of those that significantly change with our intervention, we will determine which variables are independently associated with treatment success (i.e. OSA severity <10 events per hour).

Appendix 3: Monash Health Human Research Ethics Committee approval for the Sleeping Well Trial (Version 2), Date of issue: 20/10/2015

[redacted]

MonashHealth

Research Support Services
Monash Health
Monash Medical Centre

Level 2, I Block
Australia

[redacted]

[redacted]

20 October 2015

Prof Helen Truby
Nutrition & Dietetics
Monash University
Monash Medical Centre
Block E, Level 5
[redacted]

Dear Prof Truby

Study title: Increasing the Effectiveness of Treatment for Obstructive Sleep Apnoea: The Sleeping Well Trial
SERP Ref: HREC/15/MonH/93
Monash Health HREC Ref: 15357A

The Monash Health HREC A reviewed the above application at the meeting held on 13 August 2015 In addition, the HREC is satisfied that the responses to our correspondence of 14 August 2015 have been sufficiently addressed.

The HREC approved the above application on the basis of the information provided in the application form, protocol and supporting documentation.

This reviewing HREC is accredited by the Consultative Council for Clinical Trial Research under the single ethical review system.

Approval

The HREC approval is from 20 October 2015.

Approval is given in accordance with the research conforming to the *National Health and Medical Research Council Act 1992* and the *National Statement on Ethical Conduct in Human Research (2007)*. The HREC has ethically approved this research according to the Memorandum of Understanding between the Consultative Council and the participating organisations conducting the research.

Approval is given for this research project to be conducted at the following sites and campuses:

- Monash Health, Monash Medical Centre, Clayton;
- Eastern Health, Box Hill Hospital;
- Alfred Health, Alfred Hospital

You must comply with the following conditions:

The Chief Principal Investigator is required to notify the Manager, Human Research Ethics Committees, Monash Health of:

1. Any change in protocol and the reason for that change together with an indication of ethical implications (if any)
2. Serious or unexpected adverse effects of project on subjects and steps taken to deal with them
3. Any unforeseen events that might affect continued ethical acceptability of the project
4. Any expiry of the insurance coverage provided in respect of sponsored trials
5. Discontinuation of the project before the expected date of completion, giving reasons

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Monash Health
Monash Medical Centre

Level 2, I Block
Australia

6. Any change in personnel involved in the research project including any study member resigning from Monash Health &/or the study team.

At the conclusion of the project or every twelve months if the project continues, the Principal Investigator is required to complete and forward an annual progress report to the Committee.

Reminders to submit annual progress report forms will be forwarded to the researcher.

The Coordinating Principal Investigator is responsible for notifying Principal Investigators. The Coordinating Principal Investigator and Principal Investigators should forward a copy of this letter to their site's Research Governance Officer.

The radiation procedures involved in this study are in addition to standard clinical care. The Radiation dose **does not** exceed the dose constraints specified in the Australian Radiation Protection and Nuclear Safety Agency (ARPANSA) Code of Practice for the Exposure of Humans to Ionizing Radiation for Research Purposes. However, it is a requirement that notification of the study be made to Department of Health and Human Services. This notification is to be made by each site's Radiation Safety Officer or Research Governance Unit on the Research Notification Form, within 14 days of Site Specific Authorisation being granted. A project may commence once Site Specific Authorisation has been granted.

Approved documents

Documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
National Ethics Application Form		28/7/2015
Victorian Specific Module	2	19/10/2015
Research Protocol	3	19/10/2013
Master Participant Information and Consent Form	4	19/10/2015
Consent Form	4	19/10/2015
Withdrawal of Participation Form	4	19/10/2015
DXA Scan Consent Form	2	9/10/2015
Recruitment Flowchart		
Intervention and Assessment Schedule		
Beck Depression Inventory		1966
Mood/Depression Assessment Questionnaire		
Epworth Sleepiness Scale		

Site-Specific Assessment (SSA)

SSA authorisation is required at all sites participating in the study. SSA must be authorised at a site before the research project can commence.

The completed Site-Specific Assessment Form and a copy of this ethics approval letter must be submitted to the Research Governance Officer for authorisation by the Chief Executive or delegate. This applies to each site participating in the research.

If you should have any queries about your project please contact Deborah Dell or Julie Gephart by email deborah.dell@monashhealth.org / julie.gephart@monashhealth.org

[redacted]

MonashHealth

[redacted]

Research Support Services
Monash Health
[redacted]

Level 2, I Block
Australia

[redacted]

The HREC wishes you and your colleagues every success in your research.

Yours sincerely

[redacted]

Dr James Doery
Deputy Chair - HREC

Cc: Mr Soori Thurai, Medical Physicist
Cc: MUHREC
Ms Ladan Chazi, Monash University

Checklist: Post-ethics approval requirements that must be met before a research project can commence at a study site.

Please ensure that as a PI (including the CPI) the following are completed at each study site.

Requirements	**Yes/No/NA**
Ethics approval notification The PI must send a copy to the RGO at that study site.	N/A
HREC Review Only Indemnity The PI must forward a copy of the signed HREC Review Only Indemnity to the RGO at that study site.	N/A
CTN Acknowledgement for Commercially Sponsored Studies The PI must forward a copy of the CTN Acknowledgement to Research Support Services.	N/A
CTN Lodgement for Collaborative Group/Investigator Driven Studies The PI or nominated delegate is requested to make an appointment with the Monash Health Research Support Services contact for the study deborah.dell@monashhealth.org or michael.klos@monashhealth.org so that the lodgment may be completed by both the investigator and Research Support Services. The banking details for payment to the TGA will need to be brought along to this appointment, in order to finalise notification to the TGA. The fee for lodging a CTN is $335.	N/A
SSA authorisation notification The PI must forward the SSA form and attached documents (e.g. CTRA) to the RGO so the authority approving the conduct of the trial, at that site, can complete and sign.	Yes
Radiation If applicable, the RGO must contact the Medical Physicist so that the study may be notified to the Radiation Risk Section of the Department of Health and Human Services.	Yes
Other Commonwealth statutory requirements Ensure compliance with the following e.g. Office of the Gene Technology Regulator, NHMRC Licensing Committee, NHMRC Cellular Therapies Advisory Committee.	N/A

Appendix 4: Participant Information Sheet/Consent Form for the Sleeping Well Trial (Version 10), Date of the last amendment approval: 01/03/2017

Participant Information Sheet/Consent Form

Health/Social Science Research - *Adult providing own consent*

Be Active Sleep & Eat (BASE) facility in Notting Hill

Title	*The Sleeping Well Trial: enhancing the effectiveness of continuous positive airway pressure (CPAP) treatment with a weight management program for overweight adults*
Short Title	*The Sleeping Well Trial*
Protocol Number	*HREC/15/MonH/93*
Principal Investigator	*Professor Helen Truby*
Associate Investigator(s)	*Assoc. Prof Garun Hamilton,* Ms Ladan Ghazi, *Dr Alan Young, Prof Matthew Naughton. Dr Bradley Edwards, Dr Denise* O'Driscoll, Dr Maxine Bonham, Prof Terry Haines, Dr Simon Joosten, Ms Teanau Roebuck, Ms Kirsty Yull, Ms Kaitlin Day, Dr Chiara Murgia, Mrs Kerryn Roem, Miss Kellie Hamill, Miss Claire Bristow.
Location	*Be Active Sleep & Eat (BASE) facility in Notting Hill (adjacent to Clayton campus) / Monash University*

Part 1 What does my participation involve?

1 Introduction

You are invited to take part in this research project, which is called 'The Sleeping Well Trial: enhancing the effectiveness of continuous positive airway pressure (CPAP) treatment with a weight management program for overweight adults' (Trial ID: ACTRN12616000203459). You have been invited because you have obstructive sleep apnoea and are currently recommended to undergo continuous positive airway pressure (CPAP) therapy. Your contact details were obtained from your sleep physician at Monash Medical Centre, Box Hill hospital, or the Alfred hospital, after they have informed you about this study.

This Participant Information Sheet/Consent Form tells you about the research project. It explains the processes involved with taking part. Knowing what is involved will help you decide if you want to take part in the research.

Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or local health worker.

Participation in this research is voluntary. If you don't wish to take part, you don't have to.

If you decide you want to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:

• Understand what you have read

• Consent to take part in the research project

• Consent to be involved in the research described

• Consent to the use of your personal and health information as described.

You will be given a copy of this Participant Information and Consent Form to keep.

2 What is the purpose of this research?

Obstructive sleep apnoea (OSA) is a condition in which the upper airway of patients closes off during sleep. This leads to low levels of oxygen and multiple awakenings during the night. Being overweight and having OSA are related to each other. Although not everyone with OSA is overweight, about 70% of people are and because OSA itself is an independent risk factor for cardiovascular disease, insulin resistance, Type 2 diabetes and stroke, losing weight is an important part of managing OSA.

Previous studies have shown that changing your lifestyle by diet and activity are effective ways to lose weight. However, starting CPAP is also very important and trying to both lose weight and have time to adapt to using your CPAP machine at home is challenging. We know that changing one thing at a time is often more helpful in the long term for maintaining new behaviours.

In this study we are investigating how best to support patients through a process of adaption to using CPAP and losing weight. We are trying to establish if the timing of introducing a lifestyle intervention is important to the successful management of OSA over a 12 month period. Success on this study will help us to be able to deliver interventions that support people living at home with CPAP as we will know the best time to start each intervention.

This study involves researchers from Monash University and health service partners which includes your consultant. Some of the findings from this research will be used by Ms Ladan Ghazi for a higher degree (PhD).

3 What does participation in this research involve?

A summary table of your involvement in this 12 month study is provided on page 9. Once you have provided consent, you will be eligible to enrol into the study and undergo a screening visit. For the screening visit, you will need to fast overnight.

Screening Visit (total time ~60-90 minutes)

This will involve:

- Filling in your personal information in the provided participant's data collection sheet.
- Measuring your height, blood pressure, neck circumference, and weight (using a calibrated digital scale)
- A Blood test. You will be asked if you have fasted overnight (for 10-12 hours) before coming to the session. The phlebotomist will obtain a 17 ml sample of your blood, which lets us assess your total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, glucose, insulin, leptin and other metabolites. Also it will help us examine whether life style change affects how genes are expressed at different timepoints. This is *not a genetic test* and does *not* involve identification of a gene mutation that can be transmitted to offspring.
- You will be provided with a light breakfast (cereal, fruit, milk, coffee/ tea) after the blood test.
- Completion of some questionnaires about your health status, daytime sleepiness and its effect on your quality of life, eating behaviour, activity level, health-related quality of life, depression and anxiety status.
- Group allocation. You will be randomised into one of the 6 groups in this study. The group to which you are allocated, will determine the number of months (i.e. 1-6 Months) that you will wait before starting the lifestyle intervention program. The allocated waiting time is based on randomisation and cannot be changed but everyone will receive the intervention.
- Collecting a free Fitbit Flex wireless activity and sleep tracker wristband with instructions on how to use it. As part of your involvement in this study, you are expected to use your Fitbit tracker during 12 months of the study. You will need to sign a receipt after obtaining your Fitbit tracker. We will then create a personal online account for you in Fitbit website which saves your activity history. To update the information in the website, you need to sync your tracker with your smartphone or tablet device whenever connected to Wi-Fi. By signing the consent form, you are providing us with the permission to access this data from your personal account in Fitbit Website.
- Organising an appointment to visit a CPAP clinic within 2 working days, which will assist you with commencing your CPAP therapy.
- Receiving a document folder which you can take home at the end of the session. This folder contains a fact sheet about OSA, a list of general tips for sleeping well, a copy of your signed information sheet and consent form, a flow chart that helps you to easily understand your pathway during 12 months of this study.

CPAP therapy:

At the screening visit, if you are eligible for the study, the researcher will make a time for you to visit an 'Air Liquide' outlet to receive your CPAP machine. There, you receive your CPAP education and mask fitting. The staff at Air Liquide will provide support for your CPAP treatment, in conjunction with your treating doctor. For the first week the CPAP machine will adjust its pressure automatically. Based on these initial results, the pressure will then be set to a constant level for the remainder of the study. Adjustments to the CPAP pressure

and/or mask will be at the direction of your sleep specialist in collaboration with Air Liquide. As part of your involvement in this study, you are expected to use CPAP regularly for a duration of 12 months. Overall, during 12 months of CPAP therapy, you will need to attend 5 face to face consultation sessions with Air Liquide (at time of set up, day 7, 1 month, 6 month, and 12 month), and 2 follow up calls (at 3 and 21 days following the time of set up) arranged by Air Liquide. During each consultation session, you will be asked to provide your CPAP machine and allow CPAP clinicians to extract its data. The extracted data will be uploaded in your personal account in My Vitality Club Pro which is a website developed by Air Liquide Healthcare and gives researchers and sleep physicians the possibility to access patient's clinical data and monitor their progress with CPAP therapy. The data extracted from CPAP machines will be accessible by both sleep physicians and researchers in this study. During each visit to Air Liquide CPAP clinics, you will also be asked to undergo weight measurement, using a stand on digital scale.

Lifestyle intervention program:

This is a 6 month program where we will assist you to manage your weight. The first and last (6^{th}) session of this program will be run at the Be Active Sleep Eat (BASE) facility at Notting Hill. Before attending your first and last session of the lifestyle intervention program, you will be asked to fast overnight (for 10-12 hours). When attending these two sessions, you will need to undergo weight measurement by using a calibrated digital scale. Then you will be required to undergo blood pressure measurement, followed by body measurements (i.e. waist and neck circumference). After obtaining a verbal consent, a qualified phlebotomist will collect a 17 ml blood sample. You will then be asked to provide a written consent for undergoing dual-energy x-ray absorptiometry (iDXA) scan. You will not be eligible for this test if you are pregnant. An iDXA machine will be used in this study to provide iDXA scans. An iDXA scan evaluates how much fat and muscle you have in your body. To undergo an iDXA scan, you will be required to change into a gown and remove any artefacts (e.g. jewellery, piercings, and watches). It will involve lying on a padded table for approximately 10 minutes while the scan is performed. For this study you will need to undergo two iDXA scans at two different timepoints (first and last session of the lifestyle intervention program) which both will operate by a qualified radiographer. Once the scan is completed, a copy of the iDXA scan will be provided for the study dietitian. You may also ask for a copy of your iDXA scan to keep it for your own records. After all the measurements are completed, you will be provided with a light breakfast (cereal, fruit, milk, coffee or tea). Ultimately, you will be asked to complete the same questionnaires as the screening session. The first and last session of the lifestyle intervention program will follow the same procedure which has been explained above.

Meeting with the study dietitian: During 6 months of the lifestyle intervention program, you will have monthly counselling sessions with an Accredited Practising Dietitian (APD). During the first session, the dietitian will ask you about your eating habits and describe what you will be required to do during this program which involves an active weight loss phase (initial 3 months) and maintenance phase (the second 3 months). The active weight loss phase includes diet and exercise. The diet comprises a combination of an intermittent fasting diet and a reduced energy diet (modified 5:2 fasting regimen). For the structured low energy diet days,

you will be provided with a nutrition pack, which each will last for a month. The nutrition pack consists of proportioned skim milk powder (which you will be asked to mix with skim milk/reduced fat milk at home), multivitamins with fish oil and fibre supplements. For each day of the structured low energy diet, you will be asked to use the skim milk powder with milk, multivitamin, and fish oil and fibre supplements for two meals and for the other meal you will be asked to eat a low energy meal (suitable options will be discussed with you by the dietitian). If you have not used up your allocated one-month supply of the nutrition pack, you are required to return them to the study dietitian when you come in for your next visit. You will be encouraged to schedule at least three 30 minute sessions of light physical activity (e.g. walking or jogging) each week during the 3 months of active weight loss phase. You are strongly advised to seek professional medical advice if you intend to pursue more intense physical activity. The dietitian will have access to your personal online account in Fitbit website which had been created in the beginning of the study.

You will also be asked to install the myPace App on your smartphone or tablet device to use in between consultations with the dietitian. MyPace is an app that has been developed by psychologists and its use has been shown to help people when they are trying to lose weight. It is available on the Apple App Store and Android Google Play. It will require an internet connection (Wi-Fi or mobile data) and permits communication with your dietitian. You will receive individualised 'small steps' through the app, which are simple action-based goals (e.g. eating, behaviour and physical activity oriented) that you can complete each day to help you with your weight management goals. If you do not have access to smartphone or tablet device, you will receive regular text messages or phone calls from the study dietitian.

The study dietitian will be focused on assisting you with adhering to this program. Previous participants that have completed a similar program have lost about 6kg over 3 months. Depending on your body weight after 3 months, tailored dietary advice will be provided either to help you maintain your weight lost or to lose more weight.

The first appointment will last 60 minutes, other monthly visits with dietitian last for 30 minutes and can be organised to be held either at BASE facility, or dietitian's rooms in North Fitzroy or Box Hill Hospital via the dietitian directly.

Monthly visits:

As part of your involvement in this study, you are expected to let us measure your weight every month (using a calibrated digital scale). Each visit for weight measurement may take ~5-10 minutes.

Options for weight measurement are as follows:

- At Air Liquide CPAP clinics (one month, 6 month, 12 month)
- At BASE, Box Hill Hospital, or Monash Medical Centre or Alfred Health sleep clinics
- At the dietitians rooms located in North Fitzroy or Box Hill
- If none of the venues above are suitable, a home visit may be arranged by one of the researchers

Overnight sleep study:

After 12 months of CPAP treatment, you will be scheduled for a sleep study. This visit will take about 13 hours and will allow us to see if there have been any changes in your health status and OSA severity. You will be asked to arrive at either BASE facility or your referring hospital (i.e. Monash/Eastern Health) at about 7:00 pm. We will provide you with a transportation voucher for attending the overnight sleep study. During this visit, the same questionnaires as previous visits will be completed. In addition your weight and body measurements will be assessed using a calibrated digital scale.

Your set-up for the sleep study will then start with placing leads on your body and head for measurement of heart beat, blood pressure, muscle activity, eye movements, brain activity and the level of oxygen level in the blood. Two stretchy belts will be also placed around your stomach and your chest to monitor your breathing. Two sensors will also be put under your nose (above your top lip) to measure the air that you are breathing in and out. Once all of this equipment is placed on you and you are comfortable, you will be asked to look in several directions, blink, wriggle your feet, and make chewing movements so that we can check that all of our equipment is working. We will then turn off the lights and let you go to sleep. Your breathing and sleep will be recorded until approximately 6:00 am when you will be waken up and all the study equipment, electrodes, and sensors will be removed. In morning, when you have fasted overnight for 10-12 hours, your blood pressure will be measured and subsequently, a certified phlebotomist will obtain a 17 ml sample of your blood so that we can examine your total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, glucose, insulin, leptin, cytokines, adipokines, and gene expression. Ultimately, you will be provided with a light breakfast (cereal, fruit, milk, coffee or tea).

After successfully completing the study procedure, you will be offered with a discount letter for purchasing the CPAP machine from Air Liquide and you will be able to keep the Fitbit tracker free of charge.

4 Do I have to take part in this research project?

Participation in any research project is voluntary. If you do not wish to take part, you do not have to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

If you do decide to take part, you will be given this Participant Information and Consent Form to sign and you will be given a copy to keep.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine care, your relationship with professional staff or researchers.

5 What are the possible benefits of taking part?

Currently CPAP is considered the gold standard treatment for OSA as it improves the many symptoms of the disorder and may reduce the chances of cardiovascular-related deaths.

Weight loss also helps manage OSA and 5-10% body weight loss can also reduce cardiovascular risk.

A CPAP machine and mask will be provided free of charge for all participants for use during this study by the company called *Air Liquide* (with approximate value of $1,600-$2500). Air Liquide will also provide free support to help establish you on CPAP therapy. At the end of the study the equipment needs to be returned, however you will receive a 30% discount voucher (with approximate value of $480-750) if you wish to purchase CPAP equipment from Air Liquide at the completion of the trial. If you choose to take advantage of this special offer, Air Liquide will allow you to keep the mask that you have had used during the study free of charge (with approximate value of $300). In this study, along with CPAP treatment, you will be provided with a 6-months lifestyle intervention. For your every visit to BASE facility, free parking will be provided. You will attend six monthly sessions with a dietitian (with approximate value of $600) and receive a Fitbit activity and sleep tracker (with approximate value of $100) and some liquid replacement meals and supplements for 3 months. These interventions are expected to improve your health status and OSA severity. However, we cannot guarantee that you will receive benefits from this research. You will also be provided with an overnight sleep study at no charge. Possible benefits may include improving your general health and helping others with OSA to explore more effective interventions.

6 What are the possible risks and disadvantages of taking part?

DXA: This is a X-ray and is not painful or invasive and involves a very small amount of radiation. As part of everyday living, everyone is exposed to naturally occurring background radiation and receives a dose of about 2.0 millisieverts (mSv) each year. The effective dose from this study is approximately 0.06 mSv. At this dose level, no harmful effects of radiation have been demonstrated as any effect is too small to measure.

Questionnaires and body measurements: You may feel tired after answering questionnaires and undergoing body measurements. If you do not feel ready to continue assessments, you may ask our researcher to take short breaks. You may feel that some of the questions we ask are stressful or upsetting. If you do not wish to answer a question, you may skip it and go to the next question, or you may stop immediately. If you become upset or distressed as a result of your participation in the research project, the research team will be able to arrange for counselling or other appropriate support. Any counselling or support will be provided by qualified staff who are not members of the research team. This counselling will be provided free of charge.

CPAP: CPAP is considered extremely effective at resolving OSA and is completely safe. However, some individuals may experience difficulties using the machine in the beginning; in particular some individuals may experience some level of discomfort caused by the mask that they are using. If this feeling of discomfort continues for longer than 2-3 weeks, you need to inform our researchers. You may find it difficult to use your device regularly for 12 months, but you should know that your compliance to CPAP therapy is very important and the more you use it the more benefit you gain.

Lifestyle intervention: Participants may experience tiredness or hunger after undergoing diet as a part of lifestyle intervention. This may occur due to a lower energy intake or a higher

level of physical activity, compared to your usual daily lifestyle. It will take some time for your body to get used to this program, but it is expected that those who are actively engaged in lifestyle intervention will potentially benefit from improvements in OSA severity and their general health.

Overnight sleep study: some of our patients have trouble sleeping in the sleep laboratory as it is a different environment to their usual routine. Every effort will be made to ensure patient comfort during the sleep study, but it is crucial for participants to undergo sleep study in the sleep laboratory which is a carefully controlled environment.

7 What if I withdraw from this research project?

If you do consent to participate, you may withdraw at any time. If you decide to withdraw from the project, you need to return the CPAP machine and notify a member of the research team before you withdraw. If you do withdraw, you will be asked to complete and sign a 'Withdrawal of Consent' form; this will be provided to you by the research team.

If you decide to leave the research project, the researchers will not collect additional personal information from you, although personal information already collected will be retained to ensure that the results of the research project can be measured properly and to comply with law. You should be aware that data collected up to the time you withdraw will form part of the research project results. If you do not want your data to be included, you must tell the researchers when you withdraw from the research project.

8 What happens when the research project ends?

When the research project is completed, your data will be analysed and the results will be prepared for publication in a scientific journal. If you wish to see a copy of the results of the study please contact one of the research team listed on this form. *You will be asked to fill in a short evaluation questionnaire which will assist us in planning other studies*

Part 2 How is the research project being conducted?

9 What will happen to information about me?

By signing the consent form you consent to the research team collecting and using personal information about you for the research project. Any information obtained in connection with this research project that can identify you will remain confidential. The data collected will be stored on password protected computers and in locked offices and accessed only by the research team. All information will be retained for 7 years following the completion of the study. The data collected in this study will only be used for the purpose of this research project and other future studies where the appropriate ethical approval has been obtained and it will only be disclosed with your permission, except as required by law.

The personal information that the research team collect and use is data collected through questionnaires, Fitbit trackers, physical measurements (e.g. weight and height), iDXA scans, blood samples, and sleep studies and will be stored using data storage software called LabArchives.

It is anticipated that the results of this research project will be published and/or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that you cannot be identified, except with your express permission. Your data may be presented in de-identified format or analysed as a group.

In accordance with relevant Australian and/or Victorian privacy and other relevant laws, you have the right to request access to the information about you that is collected and stored by the research team. You also have the right to request that any information with which you disagree be corrected. Please inform the research team member named at the end of this document if you would like to access your information.

Any information obtained for the purpose of this research project and for the future research that can identify you will be treated as confidential and securely stored. It will be disclosed only with your permission, or as required by law.

10 Complaints and compensation

If you suffer any distress or psychological injury as a result of this research project, you should contact the research team as soon as possible. You will be assisted with arranging appropriate treatment and support.

If you suffer any injuries or complications as a result of this research project, you should contact the study team as soon as possible and you will be assisted with arranging appropriate medical treatment. If you are eligible for Medicare, you can receive any medical treatment required to treat the injury or complication, free of charge, as a public patient in any Australian public hospital.

11 Who is organising and funding the research?

This research project is being conducted by Professor Helen Truby and her team from Monash University. It is funded partly by the department of Nutrition and Dietetics (School of Clinical Sciences) and by Dr Bradley Edwards at the Sleep and Circadian Medicine laboratory (School of psychological sciences). Air Liquide are providing the CPAP machines for 12 months.

No member of the research team will receive a personal financial benefit from your involvement in this research project (other than their ordinary wages).

12 Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC).

The ethical aspects of this research project have been approved by the HREC of Monash Health. This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2007)*. This statement has been developed to protect the interests of people who agree to participate in human research studies.

15 Further information and who to contact

The person you may need to contact will depend on the nature of your query. If you want any further information concerning this project or if you have any problems which may be related to your involvement in the project, you can contact the researcher on 9905 0187 or any of the following people:

Research contact person

Name	Professor Helen Truby
Position	Chief Investigator
Telephone	[redacted]
Email	[redacted]

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact:

Reviewing HREC approving this research and HREC Executive Officer details

Reviewing HREC name	Monash Health
HREC Executive Officer	Deborah Dell
Telephone	[redacted]
Email	[redacted]

Summary of Study Requirements

Visit	Location Options	Time and Details	What will happen
Screening visit for eligibility	Be Active Sleep & Eat (BASE) facility in Notting Hill * Free parking	~60-90 mins Appointments available between 7 and 11am appointment * Breakfast will be provided	- Blood pressure, weight, height, neck, and waist measurement - Blood test (17ml) for cardiovascular risk markers and metabolites related to OSA and changes in gene expression - Questionnaires - Collect free Fitbit activity tracker
Fitting of CPAP mask and setup CPAP machine and support sessions	Air Liquide CPAP clinic: Richmond Mon-Fri 9am-5pm Or Dandenong Mon-Fri 9:30am-4pm Sat 9:30am-2pm Or Eltham Mon – Fri 9:30am-4:00pm Sat 9:30am-2:00pm	Initial setup ~60 mins Support sessions ~30 mins	- Initial setup visit: Collect a free CPAP machine and help you to get started on CPAP - Support sessions after 7 days, 1, 6 and12 months - Receive phone calls from CPAP support team
Monthly	BASE facility * Free parking Or Monash/Eastern health Or Home visit by researcher	~10-15 mins	Weight measurement with a calibrated digital scale
Lifestyle intervention Period (6 month duration) **Timing to start will be determined by random selection**	BASE facility on Mon 10am-1pm * Free parking Or Dietitians rooms: in North Fitzroy on Wed 1am-5pm Or Box Hill hospital on Tue 2pm-5pm	Appointments are available at different places and times as follows: Initial meeting ~60-90 mins * Breakfast provided Follow-up meetings ~30 mins The myPace App is available on your smartphone which has been designed to help you meet your goals. If you do not have a smart phone the dietitian will phone you instead	**At baseline and after 6 months:** - A DXA will be performed to give you an accurate picture of your body composition - Blood pressure, weight, neck, and waist measurement - Blood test (17ml) for cardiovascular risk markers and metabolites related to OSA and changes in gene expression - Questionnaires **At every 6 monthly sessions:** - Meet with the dietitian who is available to support you to lose weight. See details of the intervention (page 4)
Overnight sleep study At the end of the study (12 months)	BASE facility sleep laboratory Or Referring hospital (Monash/Eastern health) * Free parking * Transport Vouchers	~13 hours * Breakfast provided * Collect your discount letter to purchase CPAP machine	As per screening visit plus an overnight - sleep study

Consent Form - *Adult providing own consent*

Title	*The Sleeping Well Trial: enhancing the effectiveness of continuous positive airway pressure (CPAP) treatment with a weight management program for overweight adults*
Short Title	*The Sleeping Well Trial*
Protocol Number	*HREC/15/MonH/93*
Principal Investigator	*Prof Helen Truby*
Associate Investigator(s)	*Assoc. Prof Garun Hamilton,* Ms Ladan Ghazi, *Dr Alan Young, Prof Matthew Naughton. Dr Bradley Edwards, Dr Denise* O'Driscoll, Dr Maxine Bonham, Prof Terry Haines, Dr Simon Joosten, Ms Teanau Roebuck, Ms Kirsty Yull, Ms Kaitlin Day, Dr Chiara Murgia, Mrs Kerryn Roem, Miss Kellie Hamill, Miss Claire Bristow.
Location	*Be Active Sleep & Eat (BASE) facility in Notting Hill (adjacent to Clayton campus) / Monash University*

Declaration by Participant

I have read the Participant Information Sheet or someone has read it to me in a language that I understand.

I understand the purposes, procedures and risks of the research described in the project.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I accept that de-identified data collected in this research project can be followed up or used for other studies in the future, where the appropriate ethical approval has been obtained.

I freely agree to participate in this research project as described and understand that I am free to withdraw at any time during the project without affecting my future care.

I understand that I will be given a signed copy of this document to keep.

Name of Participant (please print) _____

Signature _____ Date _____

Declaration by Researcher†

I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

Name of Researcher† (please print) _____

Signature _____ Date _____

† An appropriately qualified member of the research team must provide the explanation of, and information concerning, the research project.

Note: All parties signing the consent section must date their own signature.

Form for Withdrawal of Participation - *Adult providing own consent*

It is recommended that this form NOT be included as part of the PICF itself, but that it be developed at the same time and made available to researchers for later use, if necessary.

Title	*The Sleeping Well Trial: enhancing the effectiveness of continuous positive airway pressure (CPAP) treatment with a weight management program for overweight adults*
Short Title	*The Sleeping Well Trial*
Protocol Number	*HREC/15/MonH/93*
Principal Investigator	*Prof Helen Truby*
Associate Investigator(s)	*Assoc. Prof Garun Hamilton, Dr Alan Young, Prof Matthew Naughton. Dr Bradley Edwards, Dr Denise* O'Driscoll, Dr Maxine Bonham, Prof Terry Haines, Dr Simon Joosten, Ms Ladan Ghazi, Ms Teanau Roesbuck, Ms Kirsty Yull, Ms Kaitlin Day, Dr Chiara Murgia, Mrs Kerryn Roem, Miss Kellie Hamill, Miss Claire Bristow.
Location	*Be Active Sleep & Eat (BASE) facility in Notting Hill (adjacent to Clayton campus) / Monash University*

Declaration by Participant

I wish to withdraw from participation in the above research project and understand that such withdrawal will not affect my routine care, or my relationships with the researchers.

Name of Participant (please print) _____

Signature _____ Date _____

In the event that the participant's decision to withdraw is communicated verbally, the Senior Researcher must provide a description of the circumstances below.

Declaration by Researcher†

I have given a verbal explanation of the implications of withdrawal from the research project and I believe that the participant has understood that explanation.

Name of Researcher (please print) _____

Signature _____ Date _____

† An appropriately qualified member of the research team must provide information concerning withdrawal from the research project.

Note: All parties signing the consent section must date their own signature.

Appendix 5: 18-item Three-Factor Eating Behaviour Questionnaire (TFEQ-R18)

Project: 'The Sleeping Well Trial' Subject ID ☐☐☐☐☐☐☐☐☐

Questionnaire 1: Three-Factor Eating Questionnaire

Place an X in the box which describes you best?

Cognitive restraint		Definitely true	Mostly true	Mostly false	Definitely false
1/	I deliberately take small helpings as a means of controlling my weight	☐	☐	☐	☐
2/	I consciously hold back at meals in order not to gain weight	☐	☐	☐	☐
3/	I do not eat some foods because they make me fat	☐	☐	☐	☐
		Almost never	Seldom	Usually	Almost always
4/	How frequently do you avoid 'stocking up' on tempting foods?	☐	☐	☐	☐
		Unlikely	Slightly likely	Moderately likely	Very likely
5/	How likely are you to consciously eat less than you want?	☐	☐	☐	☐
		1 – 2	3 – 4	5 – 6	7 – 8
6/	On a scale of 1 to 8, where 1 means no restraint in eating (eating whenever you want it) and 8 means total restraint (constantly limiting food intake and never 'giving in'), what number would you give yourself?	☐	☐	☐	☐

Uncontrolled eating		Definitely true	Mostly true	Mostly false	Definitely false
7/	When I smell a sizzling steak or a juicy piece of meat, I find it very difficult to keep from eating, even if I have just finished a meal	☐	☐	☐	☐
8/	Sometimes when I start eating, I just can't seem to stop	☐	☐	☐	☐
9/	Being with someone who is eating often makes me hungry enough to eat also	☐	☐	☐	☐

		Definitely true	Mostly true	Mostly false	Definitely false
10/	When I see a real delicacy, I often get so hungry that I have to eat right away	☐	☐	☐	☐
11/	I get so hungry that my stomach often seems like a bottomless pit	☐	☐	☐	☐
12/	I am always hungry so it is hard for me to stop eating before I finish the food on my plate	☐	☐	☐	☐
13/	I am always hungry enough to eat at any time	☐	☐	☐	☐

		Only at mealtimes	Sometimes between meals	Often between meals	Almost always
14/	How often do you feel hungry?	☐	☐	☐	☐

		Never	Rarely	Sometimes	≥ 1 week
15/	Do you go on eating binges though you are not hungry?	☐	☐	☐	☐

Emotional eating		Definitely true	Mostly true	Mostly false	Definitely false
16/	When I feel anxious, I find myself eating	☐	☐	☐	☐
17/	When I feel blue, I often overeat	☐	☐	☐	☐
18/	When I feel lonely, I console myself by eating	☐	☐	☐	☐

Appendix 6: Hospital Anxiety and Depression Score (HADS)

Hospital Anxiety and Depression Score (HADS)

This questionnaire helps your physician to know how you are feeling. Read every sentence. Place an "X" on the answer that best describes how you have been feeling during the LAST WEEK. You do not have to think too much to answer. In this questionnaire, spontaneous answers are more important

A	**I feel tense or 'wound up':**	
	Most of the time	3
	A lot of the time	2
	From time to time (occ.)	1
	Not at all	0
D	**I still enjoy the things I used to enjoy:**	
	Definitely as much	0
	Not quite as much	1
	Only a little	2
	Hardly at all	3
A	**I get a sort of frightened feeling as if something awful is about to happen:**	
	Very definitely and quite badly	3
	Yes, but not too badly	2
	A little, but it doesn't worry me	1
	Not at all	0
D	**I can laugh and see the funny side of things:**	
	As much as I always could	0
	Not quite so much now	1
	Definitely not so much now	2
	Not at all	3
A	**Worrying thoughts go through my mind:**	
	A great deal of the time	3
	A lot of the time	2
	From time to time, but not often	1
	Only occasionally	0
D	**I feel cheerful:**	
	Not at all	3
	Not often	2
	Sometimes	1
	Most of the time	0
A	**I can sit at ease and feel relaxed:**	
	Definitely	0
	Usually	1
	Not often	2
	Not at all	3

D	**I feel as if I am slowed down:**	
	Nearly all the time	3
	Very often	2
	Sometimes	1
	Not at all	0
A	**I get a sort of frightened feeling like "butterflies" in the stomach:**	
	Not at all	0
	Occasionally	1
	Quite often	2
	Very often	3
D	**I have lost interest in my appearance:**	
	Definitely	3
	I don't take as much care as I should	2
	I may not take quite as much care	1
	I take just as much care	0
A	**I feel restless as I have to be on the move:**	
	Very much indeed	3
	Quite a lot	2
	Not very much	1
	Not at all	0
D	**I look forward with enjoyment to things:**	
	As much as I ever did	0
	Rather less than I used to	1
	Definitely less than I used to	2
	Hardly at all	3
A	**I get sudden feelings of panic:**	
	Very often indeed	3
	Quite often	2
	Not very often	1
	Not at all	0
D	**I can enjoy a good book or radio/TV program:**	
	Often	0
	Sometimes	1
	Not often	2
	Very seldom	3

Appendix 7: Beck Depression Inventory-second version (BDI-II)

Roche

V 0477

Beck Depression Inventory

CRTN: _____ CRF number: _____

Baseline

Page 14 patient inits: _____

BDI-II

Date:

Name: _____ Marital Status: _____ Age: _____ Sex: _____

Occupation: _____ Education: _____

Instructions: This questionnaire consists of 21 groups of statements. Please read each group of statements carefully, and then pick out the **one statement** in each group that best describes the way you have been feeling during the **past two weeks, including today**. Circle the number beside the statement you have picked. If several statements in the group seem to apply equally well, circle the highest number for that group. Be sure that you do not choose more than one statement for any group, including Item 16 (Changes in Sleeping Pattern) or Item 18 (Changes in Appetite).

1. Sadness

0 I do not feel sad.
1 I feel sad much of the time.
2 I am sad all the time.
3 I am so sad or unhappy that I can't stand it.

2. Pessimism

0 I am not discouraged about my future.
1 I feel more discouraged about my future than I used to be.
2 I do not expect things to work out for me.
3 I feel my future is hopeless and will only get worse.

3. Past Failure

0 I do not feel like a failure.
1 I have failed more than I should have.
2 As I look back, I see a lot of failures.
3 I feel I am a total failure as a person.

4. Loss of Pleasure

0 I get as much pleasure as I ever did from the things I enjoy.
1 I don't enjoy things as much as I used to.
2 I get very little pleasure from the things I used to enjoy.
3 I can't get any pleasure from the things I used to enjoy.

5. Guilty Feelings

0 I don't feel particularly guilty.
1 I feel guilty over many things I have done or should have done.
2 I feel quite guilty most of the time.
3 I feel guilty all of the time.

6. Punishment Feelings

0 I don't feel I am being punished.
1 I feel I may be punished.
2 I expect to be punished.
3 I feel I am being punished.

7. Self-Dislike

0 I feel the same about myself as ever.
1 I have lost confidence in myself.
2 I am disappointed in myself.
3 I dislike myself.

8. Self-Criticalness

0 I don't criticize or blame myself more than usual.
1 I am more critical of myself than I used to be.
2 I criticize myself for all of my faults.
3 I blame myself for everything bad that happens.

9. Suicidal Thoughts or Wishes

0 I don't have any thoughts of killing myself.
1 I have thoughts of killing myself, but I would not carry them out.
2 I would like to kill myself.
3 I would kill myself if I had the chance.

10. Crying

0 I don't cry anymore than I used to.
1 I cry more than I used to.
2 I cry over every little thing.
3 I feel like crying, but I can't.

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_____ Subtotal Page 1

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Roche

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Beck Depression Inventory

CRTN: _____ CRF number: _____ Page 15 patient inits: _____

Baseline

11. Agitation

0 I am no more restless or wound up than usual.
1 I feel more restless or wound up than usual.
2 I am so restless or agitated that it's hard to stay still.
3 I am so restless or agitated that I have to keep moving or doing something.

12. Loss of Interest

0 I have not lost interest in other people or activities.
1 I am less interested in other people or things than before.
2 I have lost most of my interest in other people or things.
3 It's hard to get interested in anything.

13. Indecisiveness

0 I make decisions about as well as ever.
1 I find it more difficult to make decisions than usual.
2 I have much greater difficulty in making decisions than I used to.
3 I have trouble making any decisions.

14. Worthlessness

0 I do not feel I am worthless.
1 I don't consider myself as worthwhile and useful as I used to.
2 I feel more worthless as compared to other people.
3 I feel utterly worthless.

15. Loss of Energy

0 I have as much energy as ever.
1 I have less energy than I used to have.
2 I don't have enough energy to do very much.
3 I don't have enough energy to do anything.

16. Changes in Sleeping Pattern

0 I have not experienced any change in my sleeping pattern.
1a I sleep somewhat more than usual.
1b I sleep somewhat less than usual.
2a I sleep a lot more than usual.
2b I sleep a lot less than usual.
3a I sleep most of the day.
3b I wake up 1–2 hours early and can't get back to sleep.

17. Irritability

0 I am no more irritable than usual.
1 I am more irritable than usual.
2 I am much more irritable than usual.
3 I am irritable all the time.

18. Changes in Appetite

0 I have not experienced any change in my appetite.
1a My appetite is somewhat less than usual.
1b My appetite is somewhat greater than usual.
2a My appetite is much less than before.
2b My appetite is much greater than usual.
3a I have no appetite at all.
3b I crave food all the time.

19. Concentration Difficulty

0 I can concentrate as well as ever.
1 I can't concentrate as well as usual.
2 It's hard to keep my mind on anything for very long.
3 I find I can't concentrate on anything.

20. Tiredness or Fatigue

0 I am no more tired or fatigued than usual.
1 I get more tired or fatigued more easily than usual.
2 I am too tired or fatigued to do a lot of the things I used to do.
3 I am too tired or fatigued to do most of the things I used to do.

21. Loss of Interest in Sex

0 I have not noticed any recent change in my interest in sex.
1 I am less interested in sex than I used to be.
2 I am much less interested in sex now.
3 I have lost interest in sex completely.

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Appendix 8: The sleeping well trial – Baseline results of the linear regression models utilised for separate examining of the association between the study variables.

DV / IV	Statistical metrics	BMI	AHI	Cognitive restraint	Uncontrolled eating	Emotional eating	BDI-II depression	HADS depression	HADS anxiety	Emotional distress (HADS total)
Sex	β			-0.34	1.82	**-2.02***	0.84	-0.4	-0.52	-0.92
	R^2			0.004	0.048	**0.112**	0.002	0.01	0.006	0.014
	95% CI			[-1.69, 1.02]	[-0.32, 3.97]	**[-3.51, -0.53]**	[-4.82, 6.5]	[-1.44, 0.64]	[-2.26, 1.23]	[-2.97, 1.14]
Age	β			-0.03	0.02	0.04	0.04	-0.01	-0.02	-0.03
	R^2			0.016	0.003	0.031	0.002	0.004	0.003	0.007
	95% CI			[-0.08, 0.03]	[-0.07, 0.11]	[-0.02, 0.11]	[-0.2, 0.28]	[-0.05, 0.03]	[-0.09, 0.06]	[-0.11, 0.6]
BMI	β			0.09	**-0.23***	-0.12	-0.04	-0.02	0.03	0.001
	R^2			0.03	**0.082**	0.04	0.000	0.004	0.001	0.000
	95% CI			[-0.04, 0.22]	**[-0.44, -0.03]**	[-0.27, 0.03]	[-0.59, 0.5]	[-0.13, 0.08]	[-0.15, 0.2]	[-0.2, 0.2]
AHI	β	**0.07***		0.004	-0.02	-0.03	0.08	0.02	0.01	0.03
	R^2	**0.109**		0.001	0.018	0.063	0.034	0.031	0.005	0.023
	95% CI	**[0.02, 0.13]**		[-0.03, 0.03]	[-0.07, 0.02]	[-0.06, 0.001]	[-0.03, 0.2]	[-0.01, 0.04]	[-0.03, 0.05]	[-0.02, 0.07]
NC	β		0.12							
	R^2		0.001							
	95% CI		[-1.25, 1.49]							
WC	β		0.13							
	R^2		0.006							
	95% CI		[-0.3, 0.57]							
Cognitive restraint	β						-0.35	-0.17	0.14	-0.03
	R^2						0.007	0.048	0.012	0.000
	95% CI						[-1.45, 0.74]	[-0.37, 0.03]	[-0.2, 0.48]	[-0.43, 0.38]
Uncontrolled eating	β						-0.19	0.03	0.17	0.2
	R^2						0.005	0.005	0.043	0.045
	95% CI						[-0.87, 0.49]	[-0.09, 0.16]	[-0.04, 0.37]	[-0.04, 0.44]
Emotional eating	β						-0.77	0.05	0.27	0.31
	R^2						0.046	0.005	0.057	0.056
	95% CI						[-1.69, 0.15]	[-0.13, 0.22]	[-0.02, 0.55]	[-0.03, 0.64]

Abbreviations: DV, dependant variable; IV, independent variable; β, Beta-Coefficient; r^2, R-squared; NC, neck circumference; WC, wrist circumference; AHI, apnoea-hypopnoea index; BDI-II, Beck depression inventory-second version; BMI, body mass index; CI, confidence interval; HADS, hospital anxiety and depression scale.

***P* <0.05 was considered statistically significant.**