THE ASSOCIATION BETWEEN SLEEP AND OBESITY AND ITS IMPACT ON HEALTH AND WELLBEING

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Abstract:

The focus of this thesis was to investigate, especially in the context of obesity, the interactions among sleep duration and quality, and adverse health outcomes.Three comprehensive studies are described in the thesis: 1. A cross-sectional epidemiological study examined factors that are associated with both short and long sleep duration among an older Chinese population, and also assessed whether there was a link between sleep duration and chronic conditions such as obesity, hypertension, and diabetes. This study showed that long sleep duration was associated with increased risk for obesity among women. Additionally, demographic, socio-economic, and medical conditions were associated with sleep duration. Identifying potential factors that affect sleep will inform future interventions for improving sleep with potential downstream effect on obesity and other chronic disorders. 2. A cross-sectional study of patients with extreme obesity indicated that the prevalence of sleep disturbance is high in this patient population. There was a positive association between sleep disturbance factors and depressive symptoms and quality of life among these individuals. The findings emphasise the importance of adequate assessment and treatment of sleep problems in this patient population. 3. A systematic review and meta-analysis assessed the effectiveness of lifestyle modification interventions on the treatment of obstructive sleep apnoea (OSA). Lifestyle interventions such as dietary and physical activity improved OSA parameters, but were insufficient to normalise them. The findings will inform the development of future interventions for OSA, and are likely to contribute to clinical guidelines for OSA management.

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The complex associations among sleep quality, anxiety-depression, and quality of life in patients with extreme obesity

Authors: **Marzieh Hosseini Araghi**, Alison Jagielski, Iraida Neira, Adrian Brown, Suzanne Higgs, G Neil Thomas, Shahrad Taheri

Accepted in SLEEP: 8/31/2013

Effectiveness of Lifestyle Interventions on Obstructive Sleep Apnea (OSA): Systematic Review and Meta-Analysis

Authors: **Marzieh Hosseini Araghi**, Yen-Fu Chen, Alison Jagielski, Sopna Choudhury, Dev Banerjee, Shakir Hussain, Neil Thomas, Shahrad Taheri

Accepted in SLEEP: 3/29/2013

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Abbreviations

AASM	American Academy Sleep Medicine
AGFI	Adjusted Goodness of Fit Index
AGRP	Agouti-Related Peptide
AHI	Apnoea Hypopnoea Index
ARC	Arcuate Nucleus
ASPS	Advanced Sleep Phase Syndrome
BM	Body Movement
BMI	Body Mass Index
CARDIA	Coronary Artery Risk Development in Young Adults
CART	Cocaine and Amphetamine Regulated Transcript
CFI	Confirmatory Fit Index
CHES	Cardiovascular Health Epidemiology Study
CI	Confidence Interval
CNS	Central Nervous System
CPAP	Continuous Positive Airway Pressure
CT	Computerised Tomography
CVD	Cardiovascular Disease
DBP	Diastolic Blood Pressure
DSPS	Delayed Sleep Phase Syndrome
EEG	Electroencephalography
EM	Eye Movement
EPESE	Established Populations for Epidemiologic Studies of the Elderly
EPOC	Cochrane Effective Practice and Organisation of Care Group
ESS	Epworth Sleepiness Scale
GBCS	The Guangzhou Biobank Cohort Study
GFI	Goodness of Fit Index
GH	Growth Hormone
HADS	Hospital Anxiety and Depression Scale
HR	Hazard Ratio
HRQoL	Health Related Quality of Life
IDF	International Diabetes Federation
IPAQ	International Physical Activity Questionnaire
IV	Inverse Variance
IWQOL-Lite	Impact of Weight on Quality of Life-Lite
ML	Maximum Likelihood
MONICA	Multinational Monitoring of Trends and Determinants in Cardiovascular Disease
MRI	Magnetic Resonance Imaging
MSH	Melanocyte Stimulating Hormone
MSLT	Multiple Sleep Latency Test
MWT	Multiple Wakefulness Test

MT	Movement Time
NHANES	National Health and Nutrition Examination Survey
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NPY	Neuropeptide Y
NREM	Non-Rapid Eye Movement
OA	Oral Appliance
ODI	Oxygen Desaturation Index
OR	Odds Ratio
OSA	Obstructive Sleep Apnoea
PFC	Prefrontal Cortex
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSG	Polysomnography
PSQI	Pittsburgh Sleep Quality Index
QoL	Quality of Life
RCT	Randomized controlled Trials
RDI	Respiratory Disturbance Index
REM	Rapid Eye Movement
REML	Restricted Maximum Likelihood Estimate
RR	Relative Risk
SAD	Seasonal Affective Disorder
SAT	Subcutaneous Adipose Tissue
SBD	Systolic Blood Pressure
SBP	Systolic Blood Pressure
SCN	Suprachiasmatic Nucleus
SD	Standard Deviation
SDB	Sleep Disordered Breathing
SEM	Structural Equation Modeling
SF-36	Short Form-36
SHHS	Sleep Heart Health Study
SRMR	Standardised Root Mean Square Residual
SSRI	Selective Serotonin Reuptake Inhibitor
SWS	Slow Wave Sleep
TSD	Total Sleep Deprivation
TV	Television
UK	United Kingdom
US	United States
VAT	Visceral Adipose Tissue
VLCD	Very low Calorie Diet
WC	Waist Circumference
WHO	World Health Organization
WHR	Waist-Hip Ratio
WSCS	Wisconsin Sleep Cohort Study

1 INTRODUCTION

1.1 Overview of sleep and its importance to health

It is generally believed that sleep is an important aspect of a healthy lifestyle. An adult spends approximately a third of his/her adult life sleeping. However, the duration and need for sleep changes across the lifespan.[1] Evidence from animal studies suggests that prolonged total sleep deprivation may lead to death; it takes about 2 to 3 weeks for totally sleep deprived rats to die.[2] The experimental evidence points towards a greater impact of short sleep duration on health and well-being as opposed to long sleep duration. As experimental studies on the effects of prolonged sleep deprivation cannot be conducted in humans, our understanding must rely on evidence from cumulative epidemiological studies and short-term experimental studies. Epidemiological evidence has, however, been conflicting. Several studies have suggested that both short and long sleep duration are associated with an increased risk for mortality.[3] The experimental evidence points towards a greater impact of short as opposed to long sleep. There are several interrelated aspects of sleep including sleep duration and quality. Increasing evidence is highlighting the importance of sleep quality as well as quantity for optimal health.[4] It is believed that the potential adverse physiological outcomes of shorter and or poor quality sleep such as obesity, diabetes, and cardiovascular may mediate the pathways between sleep and mortality.[4]

1.1.1 Sleep architecture

Electroencephalography (EEG) is commonly used to record the brain activity during sleep as part of polysomnography.[5] Polysomnographically, sleep is divided in two main types; non-rapid eye movement (NREM) and rapid eye movement (REM). Based

on recent criteria, NREM sleep is also divided into 3 stages; N1, N2, N3. In general, sleep commences with NREM sleep and proceeds from stage N1 to stage N3, followed by a stepwise return to N1, which is then followed by REM sleep (Stage R).[6] The stages are then repeated with every cycle occurring 5-7 times per night. The first NREM-REM sleep cycle is shorter than second and later cycles.[7] On average, 80% of total night-time sleep is NREM and 20% REM. N1 is a transitional phase between sleep and wakefulness. It is more likely for N1 sleep to be disrupted by external stimuli. The length of this stage is normally between 1 to 7 minutes, which contributes to approximately about 4% of total nocturnal sleep.[7] Responsiveness to external stimuli considerably decreases in N2 stage of sleep and this stage constitutes approximately 45% of sleep. N3 is commonly known as slow-wave sleep (SWS), which typically occurs in the earlier part of the night. The length of N3 sleep normally only contributes to a small percentage of total sleep time, and constitutes about 10% of sleep.[8] REM sleep is normally classified as two subdivided stages; "phasic" REM and "tonic" REM. The phasic REM consists of rapid eye movements, muscle twitches, and respiratory alterations. REM sleep is dominated by increased sympathetic nervous system activity. On the other hand, the tonic REM is dominated by parasympathetic nervous system activity. In general, it is believed that most of dreaming occurs during REM sleep. Memory processes are also more likely to be promoted in this stage.[7]

1.1.2 The mechanisms regulating sleep

The alternation between sleep and wakefulness is mainly governed by two interacting drives: circadian rhythm and homeostatic sleep drives (Figure 1-1).[9]

1.1.2.1 Circadian drive (Process C)

Circadian comes from the Latin phrase of "*circa diem"* which means "about a day". The hypothalamic suprachiasmatic nucleus (SCN), which is also known as biological clock regulates various intrinsic body rhythms.[10] The SCN synchronises daily behavioural and physiological rhythms. The regulation of body core temperature is also controlled by the SCN. A decrease in body temperature in the evening can potentially promote sleep and conversely, an increase in body temperature is associated with wakefulness in the early morning. There are several conditions such as seasonal affective disorder (SAD), advanced sleep phase syndrome (ASPS), delayed sleep phase syndrome (DSPS), and jet lag, which are related to alterations in circadian regulation.[11] Melatonin, produced by the pineal gland is a hormone that has an important role in the regulation of the human sleep-wake cycle. It has been found that melatonin secretion marks the diminution of the circadian drive for wakefulness allowing sleep to occur.[11]

1.1.2.2 Homeostatic sleep drive (Process S)

The task of the homeostatic sleep drive is often anecdotally interpreted to be similar to what happens in a bank. During wakefulness, a sleep debt accumulates, this needs to be repaid through sleeping. Thus, the homeostatic drive becomes stronger as the day progresses and when the circadian drive diminishes, sleep can proceed.[10] Prior sleep and wakefulness may influence the homeostatic drive and determine sleep need or sleep pressure. In normal conditions, sleep pressure increases during wakefulness and diminishes during sleep. However, with sleep deprivation, it increases continuously until sleep occurs. The circadian pacemaker maintains the periods of wakefulness and sleep. Daily EEG activities may also be influenced by circadian pacemaker.[8]

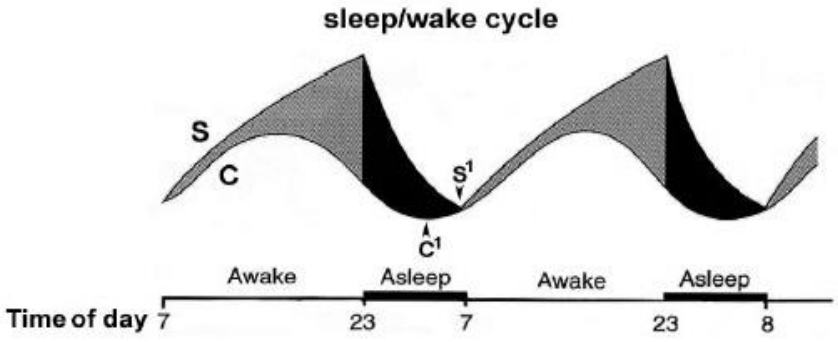

Figure 1-1. A model for the regulation sleep-wake under the influence of circadian and homeostatic drives.[9]

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1.1.3 Sleep patterns across the life span

It is known that sleep patterns change with age. In general, the mechanisms underlying onset and prolongation of sleep differ from infancy to later stages of adulthood. It is believed that there is an inverse link between sleep efficiency (a common measure for sleep quality, calculated as total sleep duration divided by time spent in bed) and age advancement. The impact of age on sleep patterns is complex and is not fully understood. Investigation of sleep characteristics across the life span may potentially help us to understand the function of sleep and develop strategies for improvement of sleep efficiency.

1.1.3.1 Newborns

Total sleep duration is markedly longer at birth. On average, the sleep duration of a newborn is between 16 to 18 hours.[12] The circadian system is not fully developed among newborns, therefore infants have three distinctive sleep types; quiet sleep (equivalent to NREM), active sleep (similar to REM) and intermediate sleep.[12] Sleep

commencement normally occurs in REM, as there is no distinct NREM. Sleep consolidation shows greater establishment at 2 to 3 months of age, when circadian rhythms mature. Control of 24-hour core body temperature, nocturnal sleep adjustment and regulation of melatonin and cortisol hormones occurs within the first three months since birth, as a result of circadian rhythm development.[13]

Sleep-wake cycles become more regular by 3 months of age. Sleep onset begins with NREM sleep with the duration of NREM-REM cycle being approximately 50 minutes. Total sleep duration significantly decreases between 6 and 12 months of age and the majority of sleep occurs in the evenings with one or two napping episode during the day.[12]

1.1.3.2 Young children and adolescents

It is believed that sleep duration decreases, as a child gets older. By 5 years of age, the total amount of sleep decreases by 2 hours.[14] Environmental changes as well physiological changes have a significant impact on sleep characteristics among young children. A reduction in the frequency of daytime napping among children aged between 3 to 5 years old could be a potential factor that contributes to reduction in sleep time. School time routines may also correlate with a decrease in time asleep.[13] Circadian sleep phase preferences appear to be consolidated by the time children enter school.[13] It has been previously found that compared to adolescents, younger children tend to have prolonged REM sleep and their sleep time in N3 sleep is relatively higher.[15]

Total sleep duration between 9 to 10 hours per night has been recommended for adolescents to have favourable performance.[15] However, the majority of individuals who are in their second decade of life sleep less than recommended amount. The

results of a large population-based study in the US demonstrated that the average sleep time of a group of students who are in secondary school is about 7.9 hours per night.[16] Sleep deprivation and excessive technology use has been reported to be significantly associated with a greater risk of obesity among UK adolescents.[17] Alteration in the regulation of hormones and initiation of puberty has been found to be associated with a reduction in SWS and a rise in N2 sleep. It has also been found that compared to earlier stages of puberty, the later stages are associated with excessive daytime sleepiness.[15]

1.1.3.3 Adults and older people

A decline in sleep consolidation and earlier arousal from sleep in the morning are considered to be two consistent sleep changes that occur at later stages of adulthood.[18] Older individuals are more likely to go to bed earlier in the evenings and also wake up at an earlier time in the mornings compared to younger individuals i.e. their sleep phase is advanced. Common causal factors for poor sleep quality in older individuals is summarised in Table 1-1. Although, the underlying reasons for early morning awakening of older adults is not known, one explanation is a positive association with light sensitivity and ageing.[18] Age-related alterations in the circadian pacemaker could also be a potential mechanism explaining why older individuals experience early awakenings.[19] Delay in the morning body temperature rise and modifications in secretion patterns of cortisol and melatonin are common consequences of age-related changes in the circadian pacemaker that could potentially increase the likelihood of early sleep arousal of older adults.[18] The episodes of awakening are normally very brief among younger individuals, occurring in REM sleep.[20] REM sleep arousals that commonly occur among younger adults suggest that there is a protective mechanism that could potentially prevent awakening in NREM sleep amongst these individuals,

and that this gradually disappears as age increased. As during SWS, arousal thresholds are in the highest range and the length of SWS may gradually decrease with ageing; therefore older individuals experience frequent early awakenings.[20]

Table 1-1. Summary of common causal factors for poor sleep quality in older individuals.

Causal factors	Examples
Physiologic	Age-related alteration in circadian rhythm, the menopause, deterioration in vision (light sensitivity), neuronal loss
Medical disorders	Arthritis, chronic cardiac or pulmonary disease, gastro-oesophageal reflux disorder, prostatic hypertrophy, medications (e.g. diuretics)
Psychiatric disorders	Depression, dementia
Primary sleep problems	Obstructive sleep apnoea (OSA), REM sleep behaviour disorder
Behavioural and social factors	Retirement (changes in wake up and sleep time), bereavement, napping
Environmental factors	Bedroom environment (e.g. noise, light, temperature, bedding)

While the ability to sleep declines with ageing, it is important to consider that the need to sleep does not appear to fade out at any stages of life span. Sleep problems are highly prevalent among older adults.[21] It has been found that disrupted sleep could negatively influence quality of life, mood and vigilance among older individuals.[21] The majority of older adults experience difficulties initiating and maintaining sleep.[22] Several health conditions such as depression, chronic respiratory disease, and physical disability may also contribute to alterations in sleep patterns of older individuals.[21] However, a reduction in sleep efficiency has been detected among 'healthy' older individuals.[23]

The impact of ageing on sleep patterns differs significantly between men and women. A decline in SWS appears to predominantly affect men. By 70 years of age, women on average spend 20 per cent of their total sleep time in N3 sleep, while men spend less than 5 per cent of their total sleep time in N3 sleep.[24] Older women have advanced body temperature rhythms, which could explain why they tend to go to bed earlier in evenings and wake up earlier in the mornings compared to older men.[20] A reduction in REM sleep is consistent with ageing and is not affected by gender. A decline in circadian rhythms contributes to a reduction in melatonin levels among older individuals. Deterioration in sleep continuity and frequent episodes of awakening may be associated with sleep homeostasis impairment among the older population.[21]

1.1.4 The measurement of sleep and associated phenomena

The current techniques for measuring sleep are summarised in Table 1-2. A self-report measure, due to its convenience, is the most common method that has been utilised to collect data on sleep, especially in large epidemiological studies. Individuals reporting sleep duration through questionnaires are generally poor at estimating sleep latency (time taken to get to sleep), sleep onset (time sleep starts), sleep duration, and sleep quality. The clearest demonstration of the inaccuracies associated with self-reported sleep measures is in insomnia. For example, findings from a study comparing subjective (using self-reported questionnaire) and objective (using polysomnography) measures of sleep perception among 92 individuals with insomnia, aged 19 to 84 years, showed that total sleep time was underestimated by a median of 81 minutes.[25] Another inaccuracy with self-reported sleep measures occurs due to individuals rounding up their sleep timings, which will affect accuracy.

Subjective sleep data may not be reliable and the possibility of recall bias cannot be completely ruled out. Recall bias could result in a differential misclassification of participants into certain categories. Ultimately, differential misclassification could result in an incorrect estimation of the association between exposure and outcome. The estimated measure of effect size can depart either towards or away from the null hypothesis as a result of recall bias of sufficient magnitude. If cases systematically report being exposed or more exposed individuals report developing a disease, the risk estimate is biased away from the null in case-control and retrospective cohort studies respectively. If, for instance, in the association between sleep duration and obesity, a great proportion of the cases are incorrectly classified as short sleepers, the association between short sleep duration and obesity may be overestimated. However, given that

the described association has not been widely reported, it would be less likely to be differentially reported. Ideally, objective measures of sleep and measurements of adiposity could minimise the effect of recall bias in this association, thus providing true estimation of the effect size.

Accurate and precise estimates of sleep parameters can be obtained via polysomnography (PSG), the 'gold standard' for measuring sleep. PSG can provide data on total sleep time, duration of each stage of sleep, number of arousals and sleep efficiency.[26] However, using PSG may not be feasible in studies with a large sample size, as this method is expensive, very time consuming and requires technical expertise. Usually, overnight PSG requires participants to sleep in the laboratory and to be attached to several electrodes which may cause sleep disruption among these individuals.[26] Population studies have been carried out successfully with PSG in the home environment, but are costly.[27]

Another objective method for collecting data on sleep is using accelerometry (actigraphy). The actigraph device is worn on the non-dominant wrist to measure movement activity and can be worn continuously for prolonged periods depending on the battery life and memory size of the device employed. Unlike PSG, actigraphy is not able to capture transition from wake to sleep and vice versa.[28, 29] Compared to PSG, actigraphy may provide more accurate and realistic information on sleep patterns, as a result of its portable and non-invasive feature which makes it practical for participants to use during their daily normal activity.[28] However, there is a high probability that the overall total sleep duration could be overestimated as a result of sedentary behaviour (e.g. sitting and watching TV). Finally, there is a need for a software programme and trained person for data synthesis.[29]

Measures of sleep such as sleep diaries could efficiently capture data on habitual sleep duration, sleep satisfaction and daytime sleepiness, but it could result in individuals overestimating their sleep duration and inaccurately reporting on their sleep quality. In general, the Pittsburgh Sleep Quality Index (PSQI)[30] and Epworth Sleepiness Scale (ESS)[31] are two validated and reliable questionnaires that may provide insight into sleep and its quality.

Table 1-2. Common techniques used to assess sleep.

Technique	Description	Advantages	Limitations
Polysomnography	A combination of electroencephalogram, electrooculogram, and electromyogram is used to obtain sleep data. Additional instrumentation is used for respiratory parameters, and behaviours and vocalizations during sleep	• Objective • Obtain data on brain activity and physiological measures • Determine sleep stages	• Not suitable for studies with large sample sizes • Intrusive • Expensive • Time consuming • Requires an expert to score data
Actigraphy	Worn on a non-dominant wrist to measure movement activity	• Objective • Inexpensive • Provides data on sleep over prolonged period	• Less accurate than PSG • Overestimates sleep duration and awakenings • Reliance on software
Sleep diary	Keeping a log of sleep-wake times and other relevant information by participants	• Inexpensive • Applicable to large samples • Provide longitudinal data	• Prone to bias • The validity and reliability of data depend on design and structure of the diary
Pittsburgh Sleep Quality Index	Categorises responses into seven sleep quality components providing a global sleep quality score	• Inexpensive • Applicable to large samples • Provides subscale and total scores of sleep quality	• Prone to bias
Epworth Sleepiness Scale	Eight-item scale assessing possibility of dozing off across eight different situations	• Inexpensive • Applicable to large samples	• Only provides information on one component of sleep (daytime sleepiness) • Not all situations are applicable to everyone

1.2 Overview of sleep and hypertension

The prevalence of hypertension has increased in the past few decades.[32] During the same period, average sleep duration has declined and evidence suggests that there is a potential link between reduced sleep and hypertension.[33] Several cross-sectional[32-36] and longitudinal[37-39] studies have previously investigated whether there is a link between sleep duration and hypertension. There is a high diversity in the findings of these studies. The results of these studies suggest that only short[34, 35, 37-39] sleep duration or both short and long sleep duration[32, 33] are associated with hypertension. Some studies have only found significant association in different age or gender groups and some have found no[36, 40] association.

In a recent large population-based study (more than 71,455 participants) Fang and colleagues[33] assessed the link between sleep duration and hypertension by age and gender among US adults. Their overall findings showed that sleep duration and hypertension interacted in U-shaped manner in the whole sample, using 8 hours sleep as the referent, (odds ratios (95% CI), <6 hours: OR 1.49, 95% CI 1.34 – 1.64, 6 hours: OR 1.15, 95% CI 1.08 – 1.23, ≥10 hours: OR 1.20, 95% CI 1.05 – 1.37) manner in the whole sample. Further analysis, stratifying for age and gender demonstrated that sleep was associated higher probability of hypertension among short sleepers (<6 hours for men, OR 1.99, 95% CI 1.52 – 2.60, women: OR 2.13, 95% CI 1.66 – 2.74) and long sleeping adults (≥10 hours for men: OR 1.56, 95% CI 1.05 – 2.32) aged 45 years or younger.[33] In a similar study, Gottlieb and colleagues[32] analysed data from Sleep Heart Health Study, which involved 2,813 men and 3,097 women, aged 40 to 100 years. Following adjustment for potential factors including age, sex, race, obesity, and apnoea hypopnoea index (AHI; a measure of obstructive sleep apnoea), the authors

found that compared with sleep duration of 7 to <8 hours per night, both middle-aged and older individuals reported sleeping less than 7 hours per night or 8 hours or more per night had higher risk for hypertension (OR 1.19, 95% CI 1.02 – 1.39 and OR 1.19, 95% CI 1.04 – 1.37, respectively). In China, Wang and colleagues[41], in a study of 1,033 men and 783 women 18 to 65 years, reported that compared to sleeping 7 to <9h, short sleep duration (<7 hours per night) in women and long sleep duration (≥9 hours per night) in men were significantly associated with increased risk of hypertension (OR 3.0, 95% CI 1.4 – 6.6 and OR 1.5, 95% CI 1.1 – 2.2, respectively). An odds ratio of 3 is a large effect that may raise the question of biological plausibility.

In the UK, results from a fully adjusted cross-sectional analysis of Whitehall II cohort study (n = 10,308)[34] showed that compared to individuals sleeping 7 hours per night, only short sleep duration (≤5 hours per night) was associated with increased risk (OR 2.01, 95% CI 1.13 – 3.58) for hypertension among women only and such a pattern was not found to be significant among men. In Norway, Bjorvatn and colleagues[35] reported in a subgroup of 8,860 participants, aged 40 to 45 years, that that the mean of both systolic and diastolic blood pressure were higher among short sleepers, but this association no longer remained significant following adjustment for gender, age and smoking and only sleep duration of 5-<6 (regression coefficient $\beta = -0.025$, $p<0.05$) and 6-<7 ($\beta = -0.027$, $p<0.05$) hours were observed to have an inverse association with systolic blood pressure compared to the reference sleep group of 7-<8 hours.

In the Rotterdam Study[36] which involved 5,058 participants aged 58 to 98 years, both self-reported measures of sleep and objective measures of sleep via actigraphy were used to assess the potential link between sleep and hypertension and the findings demonstrated that there was no association between sleep duration and hypertension.

It is difficult to interpret the temporal association between sleep and hypertension from the results of cross-sectional studies; therefore longitudinal studies may help to draw a better conclusion about a potential causal pathway between sleep and hypertension. However, like cross-sectional studies, there is diversity between findings of the available longitudinal studies investigating the role of sleep duration and incidence and progression of hypertension.

Results from the Coronary Artery Risk Development in Young Adults (CARDIA) cohort study[37] showed that after 5-year follow-up, short sleep duration was a strong predictor for the incidence of hypertension among 578 African-Americans and Whites aged 33 to 45 years (Hazard Ratio [HR] 1.37, 95% CI 1.05 – 1.78). Using data from National Health and Nutrition Examination Survey (NHANES I), Gangwisch and colleagues[38] reported that compared to 7 to 8 hours of sleep, short sleep duration (≤5 hours per night) was associated with higher risk for incidence of hypertension (HR 2.10; 95% CI 1.58 – 2.79) only among individuals between the ages of 32 and 59 years, and this association was not significant in those aged between 60 and 86 years.[38] In Korea, Kim and colleagues[39] reported that compared to sleep duration of 7 hours, short sleep duration (<5 hours per night) was associated with increased risk for incident of hypertension only among premenopausal women (HR 1.53, 95% CI 1.06 – 2.21). In a cohort study, which involved 3,608 older (≥60 years) Spanish people, Lopez-Garcia and colleagues[40] could not observe any significant association between sleep duration and incidence of hypertension.

A recent systematic review and meta-analysis[42] was conducted to quantitatively investigate the association between sleep duration and hypertension in adults. The meta-analysis included 21 studies, which represented 225,858 participants. The pooled

results from cross-sectional studies showed that compared to average sleep duration, short and long sleep duration were associated with 21% (95% CI, 1.09 - 1.34) and 11% (95% CI, 1.04 - 1.18), respectively higher risk for hypertension. The pooled results from longitudinal studies indicate that only short sleep duration was associated with increased risk of incidence and development of hypertension by 23% (95% CI, 1.06 - 1.42), but such an association was not found for long sleep duration. The authors also performed stratified analysis and examined the impact of gender on the association of sleep duration and hypertension and they found women who were short sleepers had higher risk to be hypertensive compared to men, but men who were long sleepers had higher risk for hypertension compared to women.[42]

In general, subjective measures (i.e. self-reported questionnaire) of sleep were used by the most of the studies that assessed the link between sleep duration and hypertension, although one study[36] used an objective measure of sleep (using actigraphy) and could not find any significant association between sleep and a higher risk for hypertension. The diversity of findings among these studies can be explained by differences in socio-demographic and socio-economic characteristics of the sample. It has been suggested that the positive association between sleep and hypertension, which was observed among younger individuals, is not present among older individuals. Previous evidence suggests that short sleep duration may cause alteration in endocrine and metabolism system and cause weight gain and high blood pressure.[43] It can be hypothesised that sleep loss may have different origins and have different consequences between younger and older individuals. Endogenous factors such as a fixed pattern of waking time to go to work may lead to sleep restriction among younger individuals, while the majority of older people are retired and their sleep loss may be due to other sleep problems such as insomnia.

The biological mechanism underlying the association between sleep duration and hypertension, if any, is yet to be found. It was previously suggested that short sleep duration may increase the activation of sympathetic nervous system, which may aggravate higher blood pressure.[43] Additionally, short sleep duration may change the activity of the hypothalamic-pituitary-adrenal axis which regulates the secretion of cortisol; thus sleep loss may result high blood pressure via increased elevation of cortisol.[44] It is likely that other hormones are also involved but these have not been investigated in detail.

1.3 Overview of sleep and diabetes

Several cross-sectional[45-51] and prospective[52-60] studies have previously investigated the link between sleep duration and diabetes. The results of studies are diverse, but the majority of studies suggest that short sleep duration is associated with type 2 diabetes.

In a recent cross-sectional study,[45] compared to normal sleep duration (7-8 hours), only short sleep duration (≤6 hours) was associated with higher risk for type 2 diabetes among 16,893 Chinese men and women aged 18 to 75 years (OR 1.41, 95% CI 1.07 – 1.85). In a similar study in Canada, Chaput and colleagues[46] reported that sleeping 7 hours or less was associated with diabetes (OR 1.58, 95% CI 1.13 – 2.31) among 740 men and women aged 21 to 64 years and reported that short sleepers were more likely to have higher fasting plasma glucose and insulin levels. Similar findings from a cross-sectional study[47] in Japan suggested that those sleeping 6 hours or less were more likely to have type 2 diabetes compared to those who reported sleeping 6 to 7 hours per night and such associations were independent from lifestyle and metabolic risk factors (OR 2.32, 95% CI 1.18 – 4.55).

In the US, using National Health Interview Survey data, Buxton and colleagues[48] found that both short (<7 hours) (Regression coefficient $\beta = 0.103$, $p<0.05$) and long (>8 hours) ($\beta = 0.314$, $p<0.05$) sleep duration were positively associated with diabetes. Similarly, Kachi and Colleagues[49] studied 20,744 Japanese men aged 30 to 64 years and they reported that compared to those sleeping 7 hours per night, men who reported short (≤5 hours per night) or long (≥8 hours per night) sleep duration were more likely to have untreated type 2 diabetes (OR 1.52, 95% CI 1.22 – 1.90 and OR 1.39, 95% CI 1.05 – 1.85, respectively). Findings from a cross-sectional study[50] in Finland showed that both short (≤6 hours per night) (OR 2.55, 95% CI 1.21 – 5.35) and long (≥8 hours

per night) (OR 1.76, 95% CI 1.12 – 2.61) sleep duration were associated with increased risk of type 2 diabetes among women, but the observed trend among men was not statistically significant. Knutson and colleagues[51] studied 670 men and women aged 18 to 30 years and used objective measures of sleep (using actigraphy) and they could not find any significant association between sleep duration and diabetes.

The impact of sleep on initiation and progression of diabetes has also been the main interest of several longitudinal studies. The association between self-reported sleep duration and incidence of diabetes was examined in the Nurses' Health Study[52] which involved 10-year follow-up of 70,026 American female nurses with a mean age of 52.8 years old who were free of diabetes at baseline. The results from the univariate analysis demonstrated that both compared to normal sleep duration (7-8 hours), short (≤5 hours) and long (≥9 hours) sleep duration were associated with a higher risk for the incidence of diabetes, but following adjustment for BMI and other potential confounders, the observed trend no longer remained significant for short sleep duration, and the risk of incidence and progression of diabetes was only found to be significant among long sleepers (OR 1.29, 95% CI 1.05 – 1.59). Recently, Beihl and colleagues[53] found that compared to normal sleep duration, only short sleep duration was associated with higher risk for incident of diabetes in a cohort of 900 multi-ethnic participants aged 40 to 69 years (OR 2.36, 95% CI 1.11 – 5.00).

A Swedish study[54] followed a large group of healthy men aged 35 to 51 years old. Following multivariate adjustment for potential confounders, the results demonstrated that those who reported using sleep medication to promote sleep or had sleep difficulties were more likely to have an increased risk for type 2 diabetes (OR 1.52; 95% CI 1.05 – 2.20).[54] Another similar study[55] in Sweden investigated the possible

link between sleep difficulties and onset of diabetes over a 12-year period among 1,187 men and women with no diabetes at baseline. The risk of diabetes was relatively higher among men who reported sleeping less than 5 hours per night or experienced difficulty initiating sleep (OR 2.8, 95% CI 1.1 – 7.3), but this association was not detected among women.[55]

A cohort of men from the Massachusetts Male Aging Study[56] was followed for an average of 15 years. The results demonstrated that compared to 7 hours of sleep, both short sleep duration (≤5 hours) and long sleep duration (>8 hours) were strong predictors for incidence of diabetes (RR 2.60, 95% CI 1.28 – 5.27 and RR 3.63, 95% CI 1.79 – 7.38, respectively) and the findings remained consistent even after controlling for potential covariates including; age, high blood pressure, waist circumference, education level, smoking status and self-report health status. Similarly, Gangwisch and colleagues[57] analysed data from First National Health and Nutrition Examination Survey (NHANES I) and found that those who reported sleeping 5 hours or less or 9 hours or more were more likely to develop diabetes over 8 to 10-year course of the study (RR 1.47, 95% CI 1.03 – 2.09, and RR 1.52, 95% CI 1.06 – 2.18, respectively).

The results of an 8-year prospective study from Japan,[58] demonstrated that subjective sleep disturbance (i.e. self-reported difficulty initiating sleep and/or difficulty maintaining sleep) was a strong predictor for the incidence of type 2 diabetes. Consequently, individuals who experienced frequent difficulty initiating sleep had a higher age-adjusted risk ratio for onset of type 2 diabetes (HR 2.98, 95% CI 1.36 – 6.53). The results of a prospective study in Germany[59] which involved 4,140 non-diabetic men and 4,129 non-diabetic women, aged between 25 to 74 years old showed

that difficulty maintaining sleep was associated with an increased risk for the incident of diabetes among men (HR 1.60, 95% CI 1.05 – 2.45) and women (HR 1.98, 95% CI 1.20 – 3.29). Bjorkelund and colleagues conducted a large prospective study, which involved following 1,462 Swedish women from birth for over 32 years. By the end up follow-up period, approximately 8.7% of the participants developed diabetes. No significant association was found between sleep problems and diabetes.[60]

A recent systematic review and meta-analysis[61] which involved 10 studies representing 107,756 participants estimated the risk of both sleep quantity and quality in the incidence and progression of type 2 diabetes. The pooled analysis showed that both short (≤5 hours) and long (>8 hours) sleep duration were associated with increased risk for incidence and progression of type 2 diabetes (Relative Risk [RR] 1.28, 95% CI 1.03 – 1.60) and RR 1.48, 95% CI 1.13 – 1.96, respectively). Furthermore, difficulties initiating sleep and difficulties maintaining sleep were also associated with increased risk for incidence of diabetes (RR 1.57, 95% CI 1.25 – 1.97 and RR 1.84, 95% CI 1.39 – 2.43, respectively).

Despite the variation in geographical and sample characteristics across the studies discussed, it has been consistently suggested that short sleep duration could play an important role in the onset and progression of diabetes over time and that men could be at greater risk. The main limitation of the current epidemiological studies is using subjective sleep measures (i.e. self-reported questionnaire); therefore there is an extensive need for future longitudinal studies to use objective measures of sleep (i.e. actigraphy, polysomnography) to confirm the causal role of sleep loss in progression of diabetes. Another complicating factor is that sleep is not a unitary phenomenon, but a complex state. Thus, the majority of these studies have actually found associations

that refer to “time in bed” rather than sleep per se. Evidence indicates that both “time in bed” and “time asleep” are two different dimensions of sleep duration and using one instead of the other, may result different outcomes.[62, 63]Furthermore, the focus of the studies may not have been sleep and/or diabetes, which further complicates this area of research. Nevertheless, mechanistic studies in the sleep laboratory point to a relationship between sleep loss and diabetes.[64, 65]

The potential mechanisms linking sleep duration to diabetes are yet to be fully elucidated, but are likely to involve multiple physiological pathways. It is hypothesised that short sleep duration may result an increase in activation of sympathetic nervous system which may oppose the actions of insulin, resulting in hyperglycaemia.[66] Additionally, the sleep-deprived brain may alter the activity of the hypothalamic-pituitary-adrenal axis, which results in increased secretion of cortisol, which enhances gluconeogenesis and results in insulin resistance.[67] It has also been suggested that short sleep duration would also influence regulation of appetite hormones such as leptin and ghrelin, which may increase appetite and reduce energy expenditure and facilitate weight gain and obesity and the development of insulin resistance and diabetes in the longer term. Other metabolic hormones including the incretin system have not been studied carefully in the context of sleep manipulation. Idris and colleagues,[68] however, have reported an improvement in sleepiness with the GLP-1 analogue. Exenatide, suggesting a potential relationship between GLP-1 and sleep.

1.4 Overview of obesity

Excess adiposity (obesity) has been identified as a pandemic with serious repercussions for affected individuals, health services, and economic resources.[69] The key drivers of obesity such as diet and physical activity have been the focus of numerous research studies, but the role of sleep on progression of obesity is not fully understood. Further initiatives to understand the impact of sleep improvement may draw a new opportunity to tackle obesity and may achieve greater success compared to previous interventions.

1.4.1 Definition and trends in obesity prevalence

Obesity is defined by body mass index (BMI) [as weight in kilograms divided by the square of height in meters].[70] The World Health Organization (WHO) classification of underweight, overweight and obesity in adults is presented in Table 1-3.

Table 1-3. The WHO classification of bodyweight based on BMI.*

Classification	BMI (kg/m^2) cut-off points
Underweight	<18.5
Normal weight	18.5 - 24.9
Overweight	≥25
Obese	≥30
Class I	30.0 - 34.9
Class II	35.0 - 39.9
Class III (Extreme Obesity)	≥40

* The cut-points refer to western Caucasian populations; different cut-points have been proposed for other ethnicities.

The number of people with obesity is increasing at an alarming rate in UK and worldwide.[70] According to the NHS Information Centre, in 2010, the prevalence of

obesity was 26% among both men and women, and the prevalence of overweight among men was 42% and among women was 32%.[71]

The prevalence of obesity has been previously investigated by a number of epidemiological studies.[70, 72-81] According to the results from Multinational Monitoring of Trends and Determinants in Cardiovascular Diseases (MONICA) study, the prevalence of obesity was highly varied among European countries, ranging from 7% of the male population in Sweden to 45% of female population in Lithuania.[72] The prevalence of obesity in the UK has doubled in the age group of 25 to 34 years old between the years 1993 (Male, Female 13.2% - 16.4%) to 2011 (Male, Female 23.6% - 25.9%).[73] In 2004, almost 29% of white men and 50% of black women were obese in the US.[74] The prevalence of obesity in US is continuously increasing, and it was previously estimated that the prevalence exceeds 30% across different age and sex groups. In 2009-2010 in the US, obesity was prevalent in 35.5% of men and 35.8% of women.[70] Interestingly, the prevalence of obesity in the US, which was assessed approximately two decades ago by the Third National Health and Nutrition Examination Survey (NHANES) III survey, is comparable with current obesity patterns in Europe. Obesity is also a great concern in Latin America and a higher rate of obesity was observed among women compared to men. [75] Data from a national survey in 2000, in Brazil showed that obesity affects 7.2% and 16.4% of men and women, respectively.[82]

The prevalence of obesity is also increasing in Asian countries. It was previously reported that in China, from 1993 to 2009 obesity prevalence increased in men (3% to 11%) and women (5% to 10%).[83] Interestingly, in Japan, the prevalence of obesity has not increased at the same pace as the rest of the world.[76] Data from Saudi Arabia

indicate that 29% of men and 27% of women are overweight, while obesity is prevalent in 16% of men and 24% of women.[77]

The majority of epidemiological studies that have assessed obesity prevalence are limited to one specific age group or region; therefore there might be a concern about overestimation and underestimation of prevalence. The prevalence of obesity may also vary in different socio-economic conditions or diet and lifestyle patterns.[78] A study assessing physical activity assessment in 15 European countries demonstrated that sedentary lifestyle is a very strong risk factor for obesity/overweight.[79]

Ethnicity is another factor that may increase the risk of obesity. The association between ethnicity and obesity is complex. A major consideration is methodological. The commonly used body mass index cut-points, for example, may underestimate excess adiposity in some populations e.g. the South Asian population.[84] Another consideration is the distribution of adipose tissue. For example, fat deposition is greater around the hips in Afro-Caribbeans rather than around the abdomen (visceral adiposity) where it has the greatest metabolic impact.[85] Despite methodological limitations, ethnic minority populations, appear to be at increased risk of excess adiposity and its complications such as diabetes.[86] The Health Survey for England[87] shows clearly the ethnic differences in adiposity. Regarding diabetes, for example, Indian and Pakistani men are 3 times more likely to develop diabetes compared to the general population.[87] The mechanisms mediating a potential association between ethnicity and obesity can be divided in biological and sociocultural factors. These are very briefly discussed below.

Genetics is likely to play a role in the differential deposition and distribution of adipose tissue among ethnic groups. It is likely that multiple genes are involved. Gestational

diabetes is more common amongst ethnic minorities.[88] This results in intrauterine changes that could ultimately result in obesity in the offspring through multiple mechanisms including epigenetics.[89] Other biological factors include stress and activation of the stress axis, which, in the long-term, predisposes to obesity. Differential tissue sensitivity to insulin has also been implicated. Insulin resistance results in high circulating insulin, which promotes adiposity through insulin's catabolic actions. After controlling for BMI and body composition, compared to white children, African-American children had lower insulin sensitivity (6.3 ± 0.6 vs. $4.5 \pm 0.5 \times 10^{-4}$ $min^{-1}/(\mu IU/ml)$ ($p = 0.05$).[90] Evidence suggests that biological differences may potentially increase the risk of obesity by race/ethnicity; however, the relationships are far from definitive.[90]

Minority ethnic population often experience poverty, lower socioeconomic status, lower access to education, and stigma, important factors that have been associated with obesity.[91] In some cultures, food is a dominant aspect of the identity of members of a community and there is a belief that consumption of traditional food may lower the risk of obesity.[92] Cultural factors also have an influence on preference and engagement in physical activity. For example, in a culture that parents' viewpoint is that the rest following a working day is as healthy as exercise is less likely to encourage their children to uptake physical activity for their health and wellbeing.[93] Furthermore, body image perceptions may differ among different ethnic/cultural groups. For example, perceived ideal body size is significantly larger among African women compared to whites, and African men are more likely to express higher preference for women with larger body size compared to non-Hispanic white men.[94]

It must be taken into account that it is relatively difficult to compare the prevalence of obesity among different countries, as there is significant variation in sampling and design. It has been postulated that the wide variations in obesity prevalence in Canada[80] and Sweden[81] may be attributed to immigration patterns in these countries. Based on measured data, it has reported that levels of obesity are much higher in the United States compared to England and Canada.[95]

1.4.2 The measurement of adiposity

Different measures for adiposity, which vary by feasibility, accuracy and cost, are summarised in Table 1-4. The most common measures for adiposity are BMI and waist circumference (WC). The majority of studies that previously evaluated the association between sleep and obesity in adults have used both BMI and WC, and evidence indicates that they are highly correlated (r = 0.60 – 0.80) with laboratory-based measures such as hydrometry.[96] However, neither of these measures may not accurately reflect the true estimates of health risks related to obesity. For instance, BMI is not a good representative of body fat percentage and body fat distribution and could potentially vary across different age categories, fitness and ethnicity.[97] It is known that visceral fat may result in higher health risk compared to subcutaneous fat;[96] therefore other measures than BMI should be utilised to determine visceral and subcutaneous fat. Self-reported height and weight measures were used to calculate BMI by several studies, which may introduce a serious potential bias.[97]

WC is considered to be a better measure of adiposity compared to BMI, since it is a better estimate of abdominal fat, which is a strong predictor for major health threats such as diabetes and cardiovascular complications.[98] It is more useful if WC can be used alongside BMI to estimate health risks among individuals within different BMI ranges.[99] Like BMI, WC is also unable to fully determine the differences between visceral and subcutaneous fat.[98] Measurement of WC will become more and more inaccurate with increasing adiposity as body landmarks for measurements become obscured. In order to have a better understanding of a potential link between sleep and obesity, it is very important to obtain accurate measures of body fat levels. Skin-fold thickness measurements are another measure for obesity, but these cannot be utilised

in large epidemiological studies, since it is relatively intrusive and required trained personnel.[96] The most precise and detailed information on body composition can be captured via imaging-based methods (e.g. computed tomography [CT], magnetic resonance imaging [MRI], dual energy absorptiometry [DEXA]), but these are not practical for studies with large sample size. Bio-electrical impedance devices are feasible alternatives as they are relatively inexpensive, non-invasive and portable. It has been previously reported that the accuracy of these devices are highly correlated with results from laboratory-based techniques ($r = 0.73 – 0.92$).[100] In practice, many factors such as levels of hydration and time of day interfere in accuracy and reproducibility of bioimpedance measures of body composition. Also the algorithms used by bioimpedance machines may not be true for the population under study.

Table 1-4. Summary of current measures for body fat and body composition.

Technique	Description	Advantages	Limitations
Body mass index (BMI)	BMI is calculated by dividing weight (in kilograms) by height (in metres) squared	• Inexpensive • Determines whether an individual is within healthy weight range • Applicable for both adults and children • Allows people with different body types to be within each classification • In children BMI z-scores are utilised	• Does not measure body fatness • Not appropriate for very short individuals and also pregnant women
Waist circumference	A surrogate measure for abdominal fat	• Inexpensive • Better indicator of obesity-related problem compared to BMI • Applicable for both adults and children	• Does not differentiate between subcutaneous and visceral fat • Becomes difficult to measure as adiposity increases
Skinfold thickness	A technique for determining body fat composition	• Inexpensive • Differentiate between subcutaneous and visceral fat	• Uncomfortable • Trained personnel required

Table 1-4 cont'd

Technique	Description	Advantages	Limitations
Bioelectrical impedance	Provides estimates of body fat percentage and fat-free mass	• Inexpensive • Easy and simple • Portable	• The ratio of body water to fat-free mass may alter during acute weight loss • Not as accurate as other measures • Not suitable for individuals with BMI of 35 kg/m^2 or higher
Dual energy X-ray absorptiometry	Provides two dimensional estimates of fat mass, fat-free mass, and bone mineral density	• Accurate	• Expensive • Not suitable for large sample sizes • Does not differentiate between subcutaneous and visceral fat
Imaging techniques[a]	Provide most accurate measure including	• Information on body fat distribution	• Not suitable for large sample sizes • Exposure to radiation (CT scan) • Expensive
Hydrometry	Provides fat mass, fat-free mass, and percentages of body fat using total body water	• Can be used for extreme obese individuals (BMI≥40 kg/m^2) and pregnant women	• Not suitable for large sample sizes • The ratio of body water to fat-free mass may alter during acute weight loss

[a] The imaging techniques included magnetic resonance imaging (MRI) and computerized tomography (CT).

1.4.3 Causes and consequences of obesity

In normal physiology, adipocytes store energy in the form of triglycerides.[101] An imbalance between energy input and energy expenditure could lead to hypertrophy and hyperplasia of adipocytes which results in obesity in the long run.[101] The aetiology of obesity is complex and involves multiple factors. Common risk factors for obesity are genetic predisposition and family history, metabolism, behaviour, physical activity, and the environment.[102] In recent years, other factors such as epigenetic, increased maternal age, and sleep debt have been found to be associated with obesity.[102] The mechanisms between advanced maternal age and increased risk of childhood obesity is not clear. Obesity and insulin resistance are more common in older mothers, which may affect foetal metabolism and increase the availability of nutrients to the foetus.[103] High exposure to insulin in utero results in macrosomia due to the growth-promoting effects of insulin.[104] Other factors that predispose to placental insufficiency result in small for gestational age babies.[103] Both large and small for gestational age babies are predisposed to future metabolic derangements and obesity.[104] Although not proven, epigenetic factors could also be involved.[102]

Obesity per se is known to be a risk factor for multiple health problems including cardiovascular complications, diabetes, cancer, depression, and OSA.[105] These serious health problems contribute to obesity increasing the risk of premature death (Figure 1-2).[102] It has been previously estimated that life expectancy of overweight/obese individuals is reduced significantly (approximately three years for both men and women) compared to those who are not overweight/obese and obesity at early adulthood may be a strong predictor of mortality at later stages of the lifespan.[106] The negative consequences of obesity are not limited to health but also

influence the economy. In US, it was estimated that almost 6% of annual medical expenditures which is equal to $75 billion is devoted to direct cost of obesity.[69] Moreover, the indirect cost of obesity is around $64 billion.[69] In the UK, it is also estimated that the direct cost and indirect cost of obesity are approximately £0.5bn and £2bn respectively.[107]

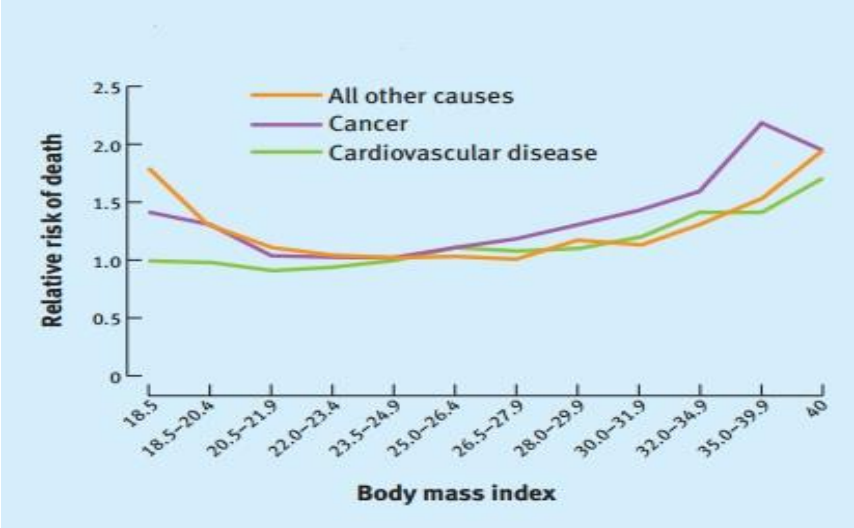

Figure 1-2. Effect of increasing BMI on premature mortality.[102]

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The causes and consequences of obesity are complex and without understanding these contributing factors to energy balance, it will not be possible to develop effective strategies to stem the rise in obesity. As a result of the complexity of obesity, it is known that a single approach to manage excess body weight will be inadequate. Sleep duration and quality may be important contributors to obesity that has been overlooked. Addressing risk factors for obesity such as sleep and conducting randomised controlled studies to assess the effect of sleep on obesity as part of a complex intervention is needed. The findings of such studies could enhance our understanding of obesity and its natural history, and allow development of preventive measures. The relationship between sleep and obesity is discussed in detail later.

1.5 Overview of sleep and obesity

The associations among sleep duration, sleep quality, and obstructive sleep apnoea (OSA), and obesity are discussed below.

1.5.1 Sleep duration and obesity

In order to tackle obesity, there is a need to identify and fully understand all the factors that contribute, to the increased risk for obesity. In recent years, a great number of studies have evaluated the link between sleep and obesity. Previous reviews[108-113] and meta-analyses[114, 115] have confirmed a positive strong link between sleep duration and obesity (Table 1-5). The findings of these reviews indicate that short sleep duration is an independent risk factor for weight gain/or obesity in both children and middle-aged individuals, but such findings have not been observed among older individuals. Different approaches have been used for data analysis by these reviews. Some of them are data synthesis of the current evidence on the association between sleep duration and obesity; some used meta-analysis, while some of them are systematic reviews of current systematic reviews. There is a mild heterogeneity among studies that are included in the two meta-analyses by Chen and colleagues[115] and Cappuccio and colleagues;[114] therefore Patel and Hu[113] did not use such analysis.

In general, all the reviews suggest that greater future research is needed to understand the nature of the association between sleep and obesity, as there is diversity among findings of different studies, which limit the interpretation of causality. Some of the reviews have highlighted several methodological problems with epidemiological evidence including measures of obesity and sleep and also confounding factors. In this section, the summary of findings from epidemiological studies is provided and then

the possible mechanisms between sleep and obesity are discussed and the limitations of these studies are addressed.

Table 1-5. Summary of recent review papers and meta-analyses on assessing a potential link between sleep and obesity.

Author, Year	Characteristics	Total number of included studies	Findings
Guidolin and Gradisar, 2012[108]	Systematic review of studies (cross-sectional and longitudinal) focusing on adolescents (age 10 to 19 years)	14 (12 cross-sectional, 2 longitudinal)	Approximately 92% of cross-sectional studies found that there is a strong link between short sleep duration and obesity, but longitudinal studies did not support these findings.
Magee and Hale, 2012[109]	Systematic reviews of longitudinal studies in adults and children	20 (13 adults, 7 children)	In children, short sleep duration was consistently observed to be an important marker of weight gain, although the results from adult studies were not consistent.
Beccuti and Pannain, 2011[110]	Literature review of epidemiological (cross sectional and longitudinal) and experimental studies in adults	21 (15 epidemiological, 6 experimental)	Both experimental and epidemiological studies have shown that both short sleep duration and poor sleep quality may potentially increase the risk of weight gain/obesity.
Nielson et al, 2011[111]	Review of systematic reviews (during year 2008), longitudinal studies in children and adults	22 (7 systematic reviews, 15 longitudinal)	Short sleep duration is a strong predictor of obesity among children, but in adults, some studies suggest only short sleep duration and some suggest that both short and long sleep duration are associated with obesity while some studies found no significant association.
Monsata et al, 2010[112]	Review of systematic reviews focused on early-life markers of obesity	23 systematic reviews	Important early-life determinants of obesity included; maternal smoking, breastfeeding, infant size and growth, television watching, and short sleep duration.

Table 1-5 Cont'd

Author, Year	Characteristics	Total number of included studies	Findings
Patel and Hu, 2008[113]	Systematic reviews of cross-sectional and longitudinal studies in children and adults	36 (31 cross-sectional, 5 longitudinal)	Results from cross-sectional and longitudinal studies consistently suggest that short sleep is associated with concurrent and future obesity. In adults, 17 out of 23 cross-sectional studies suggest a potential link between short sleep duration and obesity, however all 3 longitudinal studies suggest that short sleep duration is an independent predictor of future obesity.
Cappuccio et al, 2008[114]	Systematic review and meta-analysis of epidemiological studies (cross-sectional) in children and adults	30 (18 adults, 12 children)	Short sleep duration could potentially increase the risk for obesity in children (OR 1.89, 95% CI 1.46 – 2.43) and adults (OR 1.55, 95% CI 1.43 – 1.68). No publication bias was observed, but there was a mild heterogeneity among studies.
Chen et al, 2008[115]	Systematic review and meta-analysis of epidemiological studies (cross-sectional, case-control, longitudinal) in children	17 (12 cross-sectional, 2 case controls, 3 longitudinal)	A dose-response association exists between short sleep duration and overweight/obesity. Shortest sleep duration (OR 1.92, 95% CI 1.15 – 3.20), Much shorter sleep duration (OR 1.60, 95% CI 1.22 – 2.10), Shorter sleep duration (OR 1.43, 95% CI 1.07 – 1.91), compared to normal sleep duration (7-8 hours).

1.5.1.1 Cross-sectional studies on sleep duration and obesity

A summary of the major studies that evaluated the association between sleep duration and obesity cross-sectionally is provided in Table 1-6. In general, findings from such studies suggest that short sleep duration is positively associated with obesity. A survey by the American Cancer Society, which involved 1.1 million participants was the largest of these studies,[3] reporting that sleep duration and BMI interacted in a U-shaped manner and individuals who reported sleeping 7 hours per night had the minimum BMI. Compared to 7 hours of sleep, sleep duration of 4 hours was associated with higher BMI in both men (0.57 kg/m^2) and women (1.39 kg/m^2).[3] This association was not explored in detail in the published study that concentrated on the relation between sleep and mortality. The second largest study was by Tamakoshi and colleagues[116] in Japan, which involved over 100,000 participants. The authors reported that in both men and women, short sleep duration was associated with a reduction in BMI. The mean BMI of those who slept ≤4 hours was 22.4 kg/m^2 compared to 22.9 kg/m^2 of those who slept 7 hours.[116] To date, no other study could detect similar findings. Again, weight was not a primary outcome for this study. Results from the Sleep Heart Health Study (SHHS)[32] showed that there was a U-shaped link between sleep duration and weight. Individuals with sleep duration of 6 hours or less had greater BMI compared to those sleeping 7 to 8 hours (29.1 kg/m^2 vs. 28.4 kg/m^2). In Sweden, Bjorkelund and colleagues[60] reported that sleep duration was inversely correlated with BMI ($\beta = -0.06$) and waist-hip ratio ($\beta = -0.07$). Population-based sampling techniques were utilised by two studies. Singh and colleagues[117] analysed data from 3,158 participants and found that there was an inverse association between sleep duration and BMI, and sleep duration of 8 to 9 hours was associated with the lowest risk. Moreover, compared to sleep duration of 7-8 hours, individuals who reported to sleeping ≤5 hours (OR 1.70,

95% CI 1.31 – 2.35) and 5-6 hours (OR 1.44, 95% CI 1.12 – 1.87) per night had higher risk of being obese.[117] Similarly, in a representative sample of 1,772 men and women, Vioque and colleagues[118] found that, compared to sleep duration of 6 hours or less, those who reported sleeping 9 hours or more per night had a lower risk of being obese (OR 0.43, 95% CI 0.27 – 0.67).

In a cohort of 4,878 Brazilian truck drivers, Moreno and colleagues[119] evaluated the association between sleep and weight and found that short sleep duration (<8 hours per night) was associated with an increased the risk for obesity (OR 1.24, 95% CI 1.07 – 1.43). In a similar study, Ko and colleagues[120] analysed data from 4,793 Hong Kong union members and reported that sleep duration and BMI were inversely correlated (β = -0.03, p = 0.02). Based on data using sleep diaries, it was observed that sleep duration and BMI interacted in a U-shaped manner among 1,024 government workers in Wisconsin.[121] The results of a similar study demonstrated that each hour reduction in total sleep duration was associated with a 0.42 kg/m^2 increase in BMI among a cohort of 990 employed US adults.[122]

In a Canadian family-based cohort study, Chaput and colleagues[123] utilised several measures for obesity including; BMI, waist-hip ratio, body fat mass and skinfold thickness, and the results showed that sleep duration and obesity interacted in a U-shaped manner and compared to 7 to 8 hours sleep, men who slept 5 to 6 hours and 9 to 10 hours had 72% and 18% higher risk for obesity, and women had 63% and 51% increased risk of obesity. In France, Ohayon and Vecchierini[124] analysed data from 1,026 older (≥60 years) individuals and they reported that weight may be a predictor for short sleep duration, as their findings indicated that overweight/obese individuals (BMI>27 kg/m^2) were almost 4 times more likely to report short sleep duration

compared to those who had a BMI of 20 to 25 kg/m^2. Results of a similar study by Vorona and colleagues[125] involving 924 middle-aged American showed that longer sleep duration was prevalent among those with BMI<25 kg/m^2. Recently, Buxton and Marcelli[48] reported that self-reported sleep duration of 7 hours or less was associated with 6% of increased risk for obesity among 56,507 American adults aged 18 to 85 years.

The majority of studies to date, which have utilised subjective sleep duration (i.e. self-reported questionnaire), while several studies used objective measures (i.e. actigraphy, polysomnography) and reported mixed findings on the association between sleep duration and obesity. Lauderdale and colleagues[126] used actigraphy to evaluate the sleep patterns of 669 middle-aged participants and reported that there was no significant association between sleep duration and BMI. In a similar study, Theorell-Haglöw and colleagues[127] used overnight PSG and found an inverse correlation between sleep duration and waist circumference among 400 women who aged from 40 to 70 years (β = -1.22, p = 0.016).

In summary, evidence from cross-sectional studies suggests that short sleep duration was associated with obesity in adults. The disparity amongst studies may stem from several factors including the use of different measures of sleep and obesity, the study design, differences in the populations studied, and the statistical methods employed. It is very difficult to assess sleep duration and obesity with reliable and valid measures. The current techniques and measures of obesity and sleep have been discussed earlier. As the association between sleep and obesity has emerged slowly over a long period of time, it was not feasible to utilise detailed and more accurate methods to assess exposure and outcome for large groups of people. Other potential obstacles have been

study cost and time. Additionally, measurement errors could potentially weaken the association between sleep and obesity. For instance, measuring sleep duration using self-report methods such as sleep diaries may be prone to subjective errors. Cross-sectional studies[128-130] that used objective measures (i.e. actigraphy, polysomnography) showed stronger associations between sleep and obesity compared to those cross-sectional studies that only used self-reported data which may suggest that the results of these studies may be influenced by measurement errors.

Some potential biases may be introduced as a result of interaction between settings and measurement procedures for sleep and obesity. Self-report data may be very well-known biases that may not differ between obese and non-obese populations. The other common biases that may be less appreciated by researchers is social desirability bias that could be potentially introduced by obese individuals when answering questions on physical activity and eating habits which may lead to underestimation the obesity. The other bias, which is very difficult to prevent, is alterations in behaviours through time especially in prospective studies. Changes in behaviours such as deliberate dieting or increase in physical activity levels may also influence the results of the studies focusing on either sleep or obesity.

It is believed that ethnic difference may explain the negative association between sleep duration and obesity among Japanese. However, the effect of ethnicity has not been directly examined by many studies. It was previously found that obesity and sleep deprivation were more prevalent among African-Americans compared to Caucasions.[117, 126] Moreover, the effect of gender on sleep duration is not very clear. It was previously found that there is a link between female gender and increased susceptibility for sleep deprivation.[123, 125]

Table 1-6. Cross-sectional studies evaluating the link between sleep and obesity in adults.

Author, Year	Sample characteristics	Country	Sleep measure	Obesity measure	Results
Vioque et al, 2000[118]	1,772 M,F Age >15 years	Spain	Self-reported sleep duration "Hours of sleep per day"	BMI	≥9 hours sleep per day presented a lower probability of obesity compared to ≤6 hours sleep per day. (OR 0.43, 95% CI 0.27 – 0.67)
Shigeta et al, 2001[131]	453 M,F Mean age 53 years	Japan	Self-reported sleep duration	BMI	Short sleep duration (≤6 hours per night) was associated with increased BMI. (OR 1.98, 95% CI 1.03 – 3.82) compared to normal sleep duration (7-8 hours)
Kripke et al, 2002[3]	1.1 million M,F Mean age 57.5 years	US	Self-reported sleep duration "On average, how many hours do you sleep each night?"	BMI (calculated based on self-reported height and weight)	U-shaped association was found between sleep duration and obesity in females only, and negative association between sleep duration and obesity was found in males.
Taheri et al, 2004[121]	1,025 M,F Mean age 57.1 years	US	Polysomnography, self-reported sleep duration "How many hours of sleep do you get on work-day nights and non-work-day nights?", sleep diary	BMI	Sleep duration (sleep diary) and BMI was interacting in U-shaped manner. Short sleep duration (PSG) was associated with an increase in ghrelin. Short sleep duration (usual sleep) was associated with lower leptin.
Tamakoshi et al, 2004[116]	104,010 M,F Ages ranged from 40 to 79 years	Japan	Self-report sleep duration	BMI	Short sleep duration was associated with decreased BMI.
Bjorkelund et al, 2005[60]	1,462 F Ages ranged from 38 to 60 years	Sweden	Self-reported sleep duration "How many hours do you sleep during one 24-h period?"	BMI, WHR	Subjective sleep problems and short sleep duration (<6 hours per 24 hours) was negatively correlated with BMI and WHR. (The regression coefficient (β) = -0.06, p = 0.03 and β = -0.08, p = 0.004, respectively)

Table 1-6 Cont'd

Author, Year	Sample characteristics	Country	Sleep measure	Obesity measure	Results
Ohayon and Vecchierini, 2005[124]	1,026 M,F Mean age 60 years	France	Self-report sleep duration	BMI	A positive link was found between short sleep duration (4 hours and 30 minutes or less) and obesity (OR 3.6, 95% CI 1.0 – 13.1), compared to sleep duration of 7 hours. Short sleep duration was also associated with poor health and insomnia, which result in excessive daytime sleepiness and cognitive function impairment.
Singh et al, 2005[117]	3,158 M,F Ages ranged from 18 to 65 years	US	Self-report sleep duration	BMI	The prevalence of obesity was significantly higher among individuals with shorter sleep duration. After multivariate adjustment for potential confounders, sleep duration of 5 hours of sleep and less was associated with 40% higher risk for obesity.
Vorona et al, 2005[125]	924 M,F Mean age 48 years	US	Self-report sleep duration (bed time, wake time, and total estimated sleep time per 24 hours)	BMI	Compared to individuals with normal BMI, those who had higher BMI was more likely to report short sleep duration and also obese women reporter shorter sleep duration than obese men (434 ± 89 minutes vs. 469 ± 95 minutes).
Gottlieb et al, 2006[32]	2,813 M and 3,097 F Mean age 63.7 years	US	Self-report sleep duration "How many hours of sleep do you usually get at night (or your main sleep period) on weekdays or workdays?"	BMI	A U-shaped association was found between sleep duration and BMI.
Kohatsu et al, 2006[122]	990 M,F Mean age 48.3 years	US	Self-report sleep duration "How many hours of sleep do you get in a typical workday?"	BMI	Following multivariate adjustment, sleep duration was negatively associated with BMI among rural populations. (β = -0.42, 95% CI -0.77 – -0.07).

Table 1-6 Cont'd

Author, Year	Sample characteristics	Country	Sleep measure	Obesity measure	Results
Lauderdale et al,[126] 2006	284 M and 385 F Mean age 43.4 years	US	Actigraphy, sleep log	BMI	No significant association was observed among sleep duration and BMI (β 0.01, 95% CI - 0.02 – 0.01).
Moreno et al, 2006[119]	4,878 M Mean age 40 years	Brazil	Self-report sleep duration	BMI	Compared to 7 hours of sleep, short sleep duration (<8 hours per night) was associated with an increased risk for obesity. (OR 1.24, 95% CI 1.07 – 1.43).
Chaput et al, 2007[123]	323 M and 417 F Ages ranged from 21 to 64 years	Canada	Self-report sleep duration	BMI, WHR, skinfold thickness, body fat mass	In full adjustment, compared to 7 to 8 hours sleep, only short (5 to 6 hours per night) found to be associated with an increased risk for obesity. (OR 1.69, 95% CI 1.15 – 2.39). The association was no longer found to be significant with long sleep duration (9 to 10 hours per night) (OR 1.38, 95% CI 0.89 – 2.10).
Ko et al, 2007[120]	2,353 M and 2,440 F Mean age 42.4 years	China	Self-report sleep duration	BMI, WC	Sleep duration was inversely correlated with BMI and waist circumference (β = -0.037, p = 0.02).
Fogelholm et al, 2007[132]	7,642 M,F Mean age 54.3 years	Finland	Self-report sleep duration	BMI, WC	Compared to 7 to 8 hours sleep, short sleep duration (≤6 hours per night) was associated with an increased risk for obesity. Men (OR 1.46, 95% CI 1.13 – 1.88), Women (OR 1.75, 95% CI 1.36 – 2.25).
Buxton and Marcelli, 2010[48]	56,507 M,F Ages ranged from 18 to 85 years	US	Self-report sleep duration	BMI	Short sleepers (<7 hours sleep per night) had 6% and long sleepers (>8 hours sleep per night) had 3% higher risk for obesity compared to those who reported sleeping between 7 to 8 hours per night.

Table 1-6 Cont'd

Author, Year	Sample characteristics	Country	Sleep measure	Obesity measure	Results
Magee et al, 2010[133]	45,325 M,F Ages ranged from 55 to 95 years	Australia	Self-report sleep duration "About how many hours in each 24-hr day do you usually spend sleeping (including at night and naps)?"	BMI	A U-shaped association was found between sleep and BMI among male and female aged 55 to 64 years, but such trend was not observed among older individuals (≥65 years). <6 hours sleep (OR 1.30, 95% CI 1.10 – 1.53), ≥9 hours sleep (OR 1.17, 95% CI 1.07 – 1.26).
Anic et al, 2010[134]	5,549 F Ages ranged from 20 to 75 years	US	Self-report sleep duration	BMI	Following multivariate adjustment for potential confounders, short sleepers (<6 hours sleep per night) were 3 times more likely to be extreme obese (OR 3.12, 95% CI 1.70 – 5.75), compared to 7 hours of sleep.
Theorell-Haglow et al, 2010[127]	400 F Ages ranged from 20 to 70 years	Sweden	PSG	BMI, WC	There was as an inverse correlation between short sleep duration and obesity (β = -1.22, p = 0.016).

Female (*F*), male (*M*), polysomnography (*PSG*), body mass index (*BMI*), waist hip ratio (*WHR*), waist circumference (*WC*).

1.5.1.2 Longitudinal studies on sleep duration and obesity

A summary of major studies that evaluated the association between sleep duration and obesity longitudinally is provided in Table 1-7. The findings of such studies are inconsistent. Four studies[135-138] have reported that only short sleep duration is associated with weight gain/obesity. In a cohort which involved 496 adults and 13-year follow-up period, Hasler and colleagues[135] conducted interviews when participants were at ages of 27, 29, 34 and 40 years and the results showed that the odds ratio of obesity for short sleepers at age of 27 years was 8.2 (95% CI 1.92 – 36.30), compared to normal sleepers and the association remained persistent even after controlling for potential confounders including demographic variables, physical activity levels and family history of weight problems, and sleep duration and obesity were no longer associated after age 34 years. Using data from Nurses' Health Study, Patel and colleagues[136] found that women who reported sleeping 5 hours or less (OR 1.28, 95% CI 1.15 – 1.42) and 6 hours per night (OR 1.10, 95% CI 1.04 – 1.17) had higher odds of developing obesity (BMI>30 kg/m^2) over 16 years duration of the study compared to those reported sleeping 7 hours per night. In another study, Gunderson and colleagues[137] assessed the effects of short sleep duration on maternal postpartum weight retention among 940 women and they suggested that women slept ≤5 hours per night during 6 months postpartum period, were more likely to gain ≥5 kg weight at 1 year postpartum (OR 3.13, 95% CI 1.42 – 6.94), compared to those sleeping 7 hours. Recently, in Japan, Nishiura and Hashimoto[138] analysed data from 3,803 middle aged male workers and they reported that compared to those who reported sleeping 7 hours, those sleeping 5 hours or less were more likely to gain 0.15 kg/m^2 following multivariate adjustment for age, baseline BMI, lifestyle factors and medication (β 0.01, 95% CI 0.03 – 0.27).

Four studies[139-142] found that both short and long sleep duration were associated with an increased risk for obesity (U-shaped association). The longitudinal analysis of the Quebec Family Study[139] demonstrated that compared to the average duration sleep group (7-8 hours), short (5-6 hours) and long duration (9-10 hours) sleepers gained 1.84 kg (95% CI 1.13 – 2.62) and 1.49 kg (95% CI 0.92 – 2.48) more over the 6-year period of the study. A similar finding was found among a cohort of older individuals (≥60 years) in Spain and individuals who slept ≤5 hours (OR 3.41, 95% CI 1.34 – 8.69) and 8 hours (OR 3.77, 95% CI 1.55 – 9.17) had higher risk of severe obesity compared with individuals who slept 7 hours.[140] Recently, Hairston and colleagues[141] utilised imaging techniques to measure obesity and they found that both short and long sleep duration were associated a greater accumulation of subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT), and that such associations were only significant among those younger than 40 years. The results of a study which involved 35,247 Japanese company employees demonstrated that there was no significant association between sleep duration and obesity among women; however, among men, short sleepers and long sleepers had 5.8% higher risk of becoming obese following the 1 year course of the study (<5 hours, β 0.01, 95% CI 0.02 – 0.14 and ≥9 hours β 0.01, 95% CI 0.07 – 0.34).[142]

Finally, six studies[143-148] have reported that there was no significant association between sleep duration and obesity and among these studies, only one study conducted by Lauderdale and colleagues[144] used objective measures for sleep (using actigraphy). The inverse association between sleep and obesity was only observed by one study, which involved 1,579 Italian men, and women aged 45 to 64 years.[149]

In summary, the results from most longitudinal studies have shown that there is a temporal association between short sleep duration and higher risk for development of obesity. In line with findings from cross-sectional studies, longitudinal studies have also confirmed that such associations are stronger among younger individuals compared to older individuals. While there is as yet no scientific confirmation, it can be hypothesised that the impact of sleep duration on body weight is attenuated in long run. The other limitations of current studies are lack of adjustment for appropriate confounding variables, detection of potential mediators, and measurement pitfalls, which are going to be fully described later on this chapter.

The association between sleep duration and obesity is relatively complex and although longitudinal designs are very useful in terms of understanding causal factors, it is not clear whether short or long sleep duration can cause obesity. Future randomised controlled trials are needed to provide detailed knowledge of the role of sleep loss in causing weight gain. It is not possible to assess the chronic effects of sleep curtailment on weight change due to ethical and practical limitations. However, recent on-going randomised controlled studies have aimed to assess the impact of sleep extension on health and well-being.

Table 1-7. Longitudinal studies evaluating the link between sleep and obesity in adults.

Author, Year	Sample characteristics	Country	Sleep measure	Obesity measure	Follow-up period	Results
Hasler et al, 2004[135]	496 M,F At baseline age was 27 years	Switzerland	Self-report sleep duration	Not Reported	13 years	At age 27 years, short sleep duration had the highest odds ratio (OR 8.2, 95% CI 1.9 – 36.3) to obesity compared to ages 29, 34 and 40 years.
Gngswich et al, 2005[143]	3,208 M,F At baseline ages ranged from 32 to 49 years	US	Self-report sleep duration	BMI	8-10 years	No significant longitudinal was detected between sleep duration and change in BMI (β = -0.05, p = 0.27)
Patel et al, 2006[136]	68,183 F At baseline ages ranged from 39 to 65 years	US	Self-report sleep duration ‘‘indicate total hours of actual sleep in a 24-hour period.’’	BMI	16 years	Women who reported sleeping 5 hours or less (OR 1.28, 95% CI 1.15 – 1.42) and 6 hours per night (OR 1.10, 95% CI 1.04 – 1.17) had higher risk of a 15-kg weight gain across the course of the study compared to those sleep 7 hours.
Littman et al, 2007[145]	173 F At baseline ages ranged from 50 to 75 years	US	Self-report sleep duration	BMI	1 year	No significant association was found between sleep duration and changes in body weight.
Chaput et al, 2008[139]	276 M,F At baseline ages ranged from 21 to 64 years	Canada	Self-report sleep duration “On average, how many hours do you sleep a day?”	BMI, WC, hydrometry	6 years	Short sleepers (5-6 hours per night) gained 1.84 kg more (95% CI 1.13 – 2.62) and long sleepers (9-10 hours per night) had gained 1.49 kg more (95% CI 0.92 – 2.48) compared to 7-8 hours sleep per night.

Table 1-7 Cont'd

Author, Year	Sample characteristics	Country	Sleep measure	Obesity measure	Follow-up period	Results
Gunderson et al, 2008[137]	940 F Baseline age was not reported	US	Self-report sleep duration "In the past month, how many hours of sleep do you get in an average 24-hour period?"	BMI	1 year	Those who sleeping 5 hours were three times more likely to gain 5 kg over 6 month period compared to those who sleeping 7 hours (OR 3.13, 95% CI 1.42 – 6.94).
Lopez-Garcia et al, 2008[140]	3,235 M,F At baseline mean age of 60 years and above	Spain	Self-report sleep duration "How many hours do you usually sleep per day (including sleep at night and during the day)?"	BMI	2 years	There was a U-shaped association between sleep duration (≤5 hours vs. 7 hours, OR 3.41, 95% CI 1.34 – 8.69 and 9 hours vs. 7 hours, OR 3.77, 95% CI 1.55 – 9.17) and ≥5 kg weight gain among women, but such trend was not observed among male and total participants.
Stranges et al, 2008[146]	4,378 M,F At baseline ages ranged from 35 to 55 years	England	Self-report sleep duration	BMI	5 years	There was no link between short sleep duration (≤5 hours per night) and changes in BMI.
Lauderdale et al, 2009[144]	612 M,F At baseline ages ranged from 33 to 45 years	US	Actigraphy	BMI	5 years	No significant association was found between sleep duration and BMI.
Hairston et al,2010[141]	1,107 M,F At baseline ages ranged from 18 to 81 years	US	Self-report sleep duration "On average, about how many hours of sleep do you get a night?"	Imaging techniques (computed tomography)	5 years	A U-shaped association was found between sleep duration and BMI only among those who aged 40 years or younger.

Table 1-7 Cont'd

Author, Year	Sample characteristics	Country	Sleep measure	Obesity measure	Follow-up period	Results
Marshall et al, 2010[147]	2,091 M,F At baseline ages ranged from 37 to 60 years	Sweden	Self-report sleep duration "How many whole hours during the night do you usually sleep?"	BMI	10 years	No significant association was found between sleep duration and changes in weight.
Nishiura and Hashimoto, 2010[138]	3,803 M At baseline ages ranged from 40 to 59 years	Japan	Self-report sleep duration "How many hours, on average, do you sleep each night?"	BMI	4 years	Compared to those who sleeping 7 hours per night, short sleepers (≤5 hours sleep) had increased risk for obesity (β 0.01, 95% CI 0.03 – 0.27).
Watanabe et al, 2010[142]	34,852 M,F At baseline ages ranged from 30 to 60 years	Japan	Self-report sleep duration "How many hours do you sleep on weekdays (workdays)?" "How many hours do you sleep on the weekend (non-workdays)."	BMI	1 year	A U-shaped association was found between sleep duration (<5 hours, β 0.01, 95% CI 0.02 – 0.14 and ≥9 hours β 0.01, 95% CI 0.07 – 0.34) and BMI among men, but not among women.
Bo et al, 2011[149]	1,597 M,F At baseline, ages ranged from 45 to 64 years	Italy	Self-reported sleep duration	BMI	6 years	An inverse association was detected between sleep duration and BMI.
Nagai et al, 2013[148]	13,6296 M,F At baseline, ages ranged from 40 to 79 years	Japan	Self-reported sleep duration	BMI	10 years	No association was observed between sleep duration and weight gain. Only long sleep duration was a strong predictor of 5-kg weight gain among obese individuals (OR 1.36, 95% CI: 1.09 - 1.70).

Female (*F*), male (*M*), polysomnography (*PSG*), body mass index (*BMI*), waist circumference (*WC*)

1.5.2 Consideration of confounding variables

A major obstacle in drawing definitive conclusions for causal link between exposure and outcome in epidemiological studies is confounding by other factors. Previous reviews[71, 110] have recognised multiple potential confounding factors for the relationship between sleep duration and obesity. These factors include: age, alcohol consumption, caffeine consumption, smoking, physical activity levels, television viewing, video gaming, chronic diseases, and psychological problems. Yet there are important limitations for inclusion of appropriate confounding variables. The conflicting results of the studies that assessed the association between sleep duration and obesity could be attributable to the great variation in the confounders included in the analyses. Different confounders that have been adjusted for among studies showing U-shape association between sleep duration and obesity is summarised in Table 1-8.

The majority of these studies are controlled for age, gender, exercise, smoking, and alcohol consumption. Depression and emotional health appear to be more strongly associated with BMI than short sleep duration,[150] but only two studies have controlled for these factors. Work-related factors are another factors that are not considered. Shift work could be a prime reason for obtaining insufficient sleep[151] and only two studies adjusted for that variable. Furthermore, the literature assumes short sleep duration is a choice[152] and little attention has been paid to the role of sleep disorders and in particular sleep apnoea, a common condition, which can influence sleep duration.[153] In fact, one plausible explanation for the association between long sleep duration and weight gain is due to the confounding effect of obstructive sleep apnoea.[153] Increased pro-inflammatory cytokines in individuals with sleep apnoea may contribute to sleepiness and develop obesity in long run.[154] Only one study adjusted for sleep

problems (waking up during sleep and the use of anxiolytic medication). Lopez-Garcia and colleagues[140] found that compared to 7 hours of sleep, women sleeping ≤5 hours, (OR 3.41, 95% CI 1.34 - 8.69), 8 hours (OR 3.03, 95% CI 1.29 - 7.12) and 9 hours (OR 3.77, 95% CI 1.55 - 9.17) were more likely to have weight gain of ≥5 kg; a similar trend was not observed in men or in the total study participants. Only one study adjusted for that variable. Lopez-Garcia and colleagues[140] found that compared to 7 hours of sleep, women sleeping ≤5 hours, (OR 3.41, 95% CI 1.34 - 8.69), 8 hours (OR 3.03, 95% CI 1.29 - 7.12) and 9 hours (OR 3.77, 95% CI 1.55 - 9.17) were more likely to have weight gain of ≥5 kg; a similar trend was not observed in men or in the total study participants. Controlling for snoring, Lauderdale and colleagues[144] found no significant association between sleep duration and change in BMI ($p>0.05$). Controlling for sleep medication, Stranges and colleagues[146] found no significant association between sleep duration and changes in BMI ($\beta = -0.06$, 95% CI -0.26 - 0.014).

Table 1-8. Summary of confounding variables that are controlled for in studies showing U-shape negative association between sleep duration and risk of obesity.

	Kripke et al, 2002[3]	Taheri et al,2004[121]	Gottlieb et al, 2006[32]	Chaput et al, 2008[139]	Lopez-Garcia et al, 2008[140]	Hairston et al, 2010[141]	Watanabe et al, 2010[142]	Magee et al, 2010[133]
Age	X	X	X	X	X	X	X	X
Gender	X	X	X	X	X	X	X	X
Race	X					X		X
Education	X			X		X		X
Total income			X	X				
Occupation	X			X				
Marital status	X							X
Exercise	X			X	X	X	X	X
Smoking intake	X		X	X	X	X	X	X
Alcohol consumption			X	X	X		X	X
Coffee consumption			X	X	X			
Baseline fat						X		
Total calories						X		
Arousal from sleep					X			
Perceived health	X				X			
Leg pain	X							
History of chronic disease					X			X
History of heart disease	X		X					
History of hypertension	X							
History of cancer	X							
History of diabetes	X		X					
History of psychological distress								X
Shift worker				X			X	
Depression			X		X			
Sleeping disorders					X			

Finally, evidence suggests short sleep and obesity also may be related to the amount of time spent watching television and using social media. Media use was not adjusted for in any of the adult studies, while 63% of children studies controlled for this covariate. In recent years, the use of media is increased extensively worldwide, and the early evidence indicates that television viewing is associated with both sleep and obesity. In the US, in 2009, television compromised 58% of total media use for youths.[155] It would seem essential that a broader range of media use as well as television viewing be routinely included as potentially confounding variables. It has been reported that a combination of low sleep and high television viewing in children are associated with increased risk of being overweight at 2 years old (OR 2.00, 95% CI 1.19 – 3.36).[156]

It can be difficult to distinguish between a confounder and a mediator. Generally, a tentative distinction is made based on the interpretation of the results of the analyses. A mediator is a variable that lies on the casual pathway between a predictor of interest and the outcome, and thus to mediate the predictor's effect.

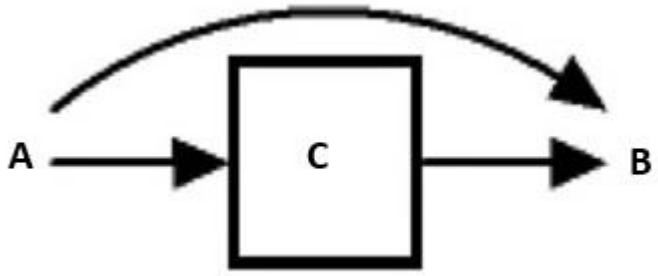

Figure 1-3. A simple statistical mediation model

In the figure above (Figure 1-3), by using simple regression technique, one can estimate the total causal effect of exposure A on outcome of B, by ignoring the intermediate variable of C. However, if one controls (i.e. adjust, stratifies, restricts) for the intermediate C, which is on causal pathway between exposure A and outcome B, the total effect of the exposure and the outcome cannot be fully estimated. The observed association between exposure A and outcome will typically be a null-biased estimate of the total causal effect, after controlling for the intermediate C. As discussed by Patel and Hu,[113] sleep deprivation is associated with higher calorie intake because of increased appetite. Increased opportunity to eat because of a drop in body temperature and increased fatigue, may lead to less physical activity and lower energy expenditure. If this hypothetical model were true and provided a mechanism by which sleep duration mediates the development of obesity, then adjustment for any of the factors above would diminish or obscure the association between sleep duration and obesity.

1.5.3 Sleep quality and obesity

In recent years, the importance of sleep quality as well as sleep quantity and its impact on health and wellbeing has been appreciated in a number of studies. Cross-sectional[127, 157, 158] and longitudinal[159, 160] studies have found that poor sleep quality was associated with an increased risk for obesity.

In a cross-sectional study, Jennings and colleagues[157] studied 210 participants (57% men) with a mean age of 46 years and they found that Pittsburgh Sleep Quality Index (PSQI) global scores was significantly associated with increased BMI ($\beta = 0.19$, $p<0.001$) and all the other components of metabolic syndrome (OR 1.44, 95% CI 1.01 - 2.06).

The results of a recent cross-sectional study[127] involving 400 adult women demonstrated that both sleep duration and sleep quality, defined by sleep efficiency and sleep architecture (minutes of SWS and REM sleep) were inversely associated with waist circumference following multivariate adjustment for potential confounders including age, physical activity level, smoking, alcohol consumption and apnoea hypopnoea index (AHI) (SWS, adj. $\beta = -0.058$ cm/min; $p = 0.025$, REM $\beta = -0.062$ cm/min; $p = 0.002$). However, such associations were less robust among older age women (age >50 years).[127]

Bidulescu and colleagues[158] analysed data from the Cardiovascular Health Epidemiology Study (CHES) which involved 1,515 African-American aged 30-65 years. They found that poor sleep quality (measured using PSQI) was associated with increased BMI in women only (OR 1.08, 95% CI 1.03 – 1.12). The authors suggested

that such an association may have been mediated by stress.[158] The impact of gender on the association of poor sleep quality and obesity has been confirmed in a longitudinal study conducted among 7,000 Finnish adults who aged between 40 to 60 years old.[159] The findings demonstrated that sleep problems including trouble falling asleep (OR 1.65, 95% CI 1.22 – 2.22), early awakening (OR 1.48, 95% CI 1.16 –1.89) and trouble maintaining asleep (OR 1.41, 95% CI 1.13 – 1.75) were strong predictors of major weight gain over the 5 to 7 year course of the study.[159] Using data from the Alameda county study, Nordin and Kaplan examined the impact of different stages of sleep discontinuity on body weight over 30 years among 7,000 middle-age adults.[160] Based on subjective measures (using self-reported questionnaire), study participants were assigned into four categories (sleep continuity, good sleep continuity, discontinuity, impaired discontinuity). After adjusting for potential confounders such as demographic and lifestyle factors, sleep discontinuity was associated with 70% (95% CI 1.04 –2.90) increased risk for transition to obesity.[160]

Sleep quality is a complex phenomenon and is difficult to define and objectively measure. Sleep duration, sleep latency, or the number of awakenings can be classified as quantitative aspect of sleep quality, and other aspects such as "depth" or "restfulness of sleep" are subjective aspects. PSG and actigraphy measures of sleep quality include sleep onset latency, sleep efficiency (time asleep over total time in bed), wake after sleep onset (amount of wakefulness after sleep has been initiated), and sleep duration.

As stated earlier, evidence suggests that both shorter sleep duration and poor sleep quality are associated with a higher risk of obesity as well as several other adverse health outcomes such as hypertension, diabetes, and cardiovascular complications

among individuals with different age, ethnicity, and socioeconomic background.[113, 114] However, the psychosocial consequences of poor sleep have been underestimated. These may, for example, predispose to maladaptive eating such as emotional food intake, and anhedonia, which may result in reduced physical activity.

1.5.4 Obstructive sleep apnoea and obesity

Obstructive sleep apnoea (OSA) is defined as complete or partial obstruction of upper airways followed by increased respiratory effort to make the airways patent again. Intermittent hypoxia accompanies the frequent episodes of cessation/reduction in airflow. Evidence indicates that an increase in body weight plays an important role in the incidence and progression of OSA. Results from the Wisconsin Sleep Cohort study suggest that a 10% weight gain from baseline to the end of the follow-up was associated with a 6 times greater risk for the development of OSA.[161]

As the prevalence and severity of obesity is increasing, it would be expected that the prevalence of other obesity-related conditions including OSA would potentially increase at the same pace. It was previously reported that in the US, OSA is prevalent in 4% of men and 2% of women, but a rise in the prevalence of obesity has also led to an increase in prevalence of OSA among obese individuals (affecting 84% men and 72% women in one study[162]). It is believed that obesity may lead to OSA through several mechanisms: 1) alterations of the upper airway structure by increased fat deposition around the neck area, 2) decreased neural compensation and increased susceptibility to airway, 3) instability of the respiratory control system, 4) respiratory muscle weakness, and 5) instability of caudal traction as a result of reduced functional residual capacity.[163]

It is known that obesity may play an important role in the development of OSA, but recently it has been suggested that OSA itself may also increase the risk for obesity. Prolonged sleep loss, sleep disturbance, and daytime sleepiness associated with OSA may result in excessive weight gain, which can thus worsen obesity. There are several

hypotheses that may explain how OSA leads to obesity: 1) reduced basal energy expenditure could potentially contribute to excessive weight gain among individuals with OSA,[164] 2) higher preference for energy dense food and increased calorie intake, 3) OSA may also be associated with alterations in the regulation of appetite hormones,[165] and 4) excessive daytime sleepiness and reduced physical activity levels.[166]A potential mechanism that may likely works as a vicious cycle on association between OSA and obesity is presented in Figure 1-4.

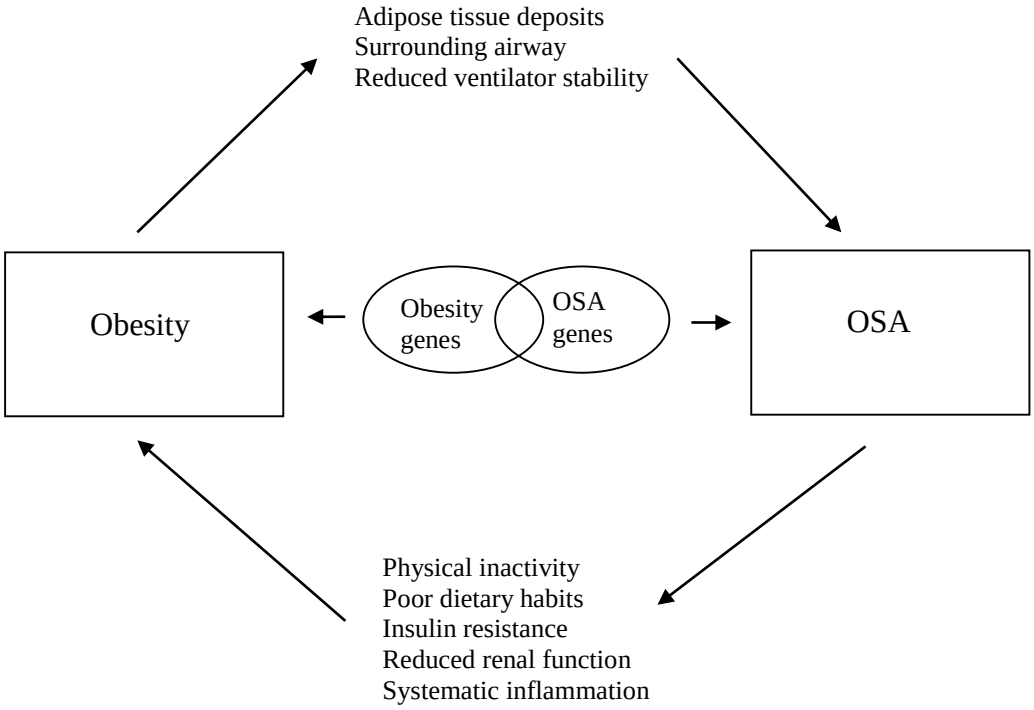

Figure 1-4. Potential mechanisms that may likely works as a vicious cycle in the pathogenesis of OSA and obesity.[167]

Used with permission from Dr Carter.

Evidence also suggests that obesity can effect sleepiness independent of OSA.[154] Vgontzas and colleagues[168] previously assessed the subjective sleepiness of 73 obese

patients without OSA compared with 45 healthy controls with normal weight. The results showed that compared with controls, obese patients were sleepier during the day and also their night sleep was more disrupted. In addition, individuals were provided with 2 daytime napping opportunities. Compared to controls, obese patients had shorter sleep latency, less awakening after onset of sleep during the nap time, longer sleeping time, and more REM sleep ($p<0.001$).[168] In a similar study, Resta and colleagues evaluated the sleep quality, sleep-related symptoms and excessive daytime sleepiness in 78 severely obese patients, ages 16 to 75 years without sleep apnoea and in 40 healthy matched controls. The findings showed that loud snoring was present in 46.7% and 8.1% of obese patients and control individuals respectively ($p<0.01$). Moreover, excessive daytime sleepiness was reported by 34.7% of the obese, but only 2.7% of the control individuals ($p<0.01$).[169] As the findings of these studies suggest that obese patients without OSA had higher levels of daytime sleepiness and they were habitual snorers, thus it can be hypothesised that snoring may contribute to sleepiness among obese people. It was previously found that snoring per se is a risk factor of daytime sleepiness independent of obesity and OSA.[170] In contrast, the effect of obesity independent of diabetes on daytime sleepiness is less well understood. Recently, it has been reported that pharmacological intervention, which could result in weight reduction and improved glycaemic control, has a significant reduction in sleepiness in diabetic obese patients without OSA.[68]

Despite the high prevalence of OSA among obese individuals, the condition is largely undiagnosed and untreated. Under recognition of the disorder in both public and clinical settings may lead to multiple adverse social and health outcomes such as road

and work accidents that may cause premature death.[171] Continuous positive airway pressure (CPAP) is known as the gold standard treatment for OSA treatment and is recommended by the national and international guidelines. However, adherence to CPAP has been found to be suboptimal.[172] Evidence suggests that weight loss may reduce the severity of OSA. Bariatric surgery is recommended for those with the greatest severity of obesity and accompanying co-morbidities.[173] Indeed, severe OSA is considered to be an indication for bariatric surgery. Bariatric surgery, however, is not without risk, is not widely available, and its long-term outcomes are unknown. For the majority of patients with OSA, lifestyle change and weight loss are recommended by guidelines,[174] but supportive evidence for this recommendation remains unexamined through systematic review and meta-analysis.

1.5.5 Potential mechanisms explaining sleep-obesity link

The underlying mechanisms mediating the link between sleep and obesity are complex and not fully understood. According to a hypothesised model by Taheri,[175] sleep loss may result in 2 major changes: 1. An alteration in regulation of appetite hormones which could result in higher food intake; and 2. Fatigue that may lead to a decrease in physical activity (Figure 1-5). Insulin resistance as a result of weight gain would also contribute to greater adiposity. Several potential mechanisms have been examined and are discussed below.

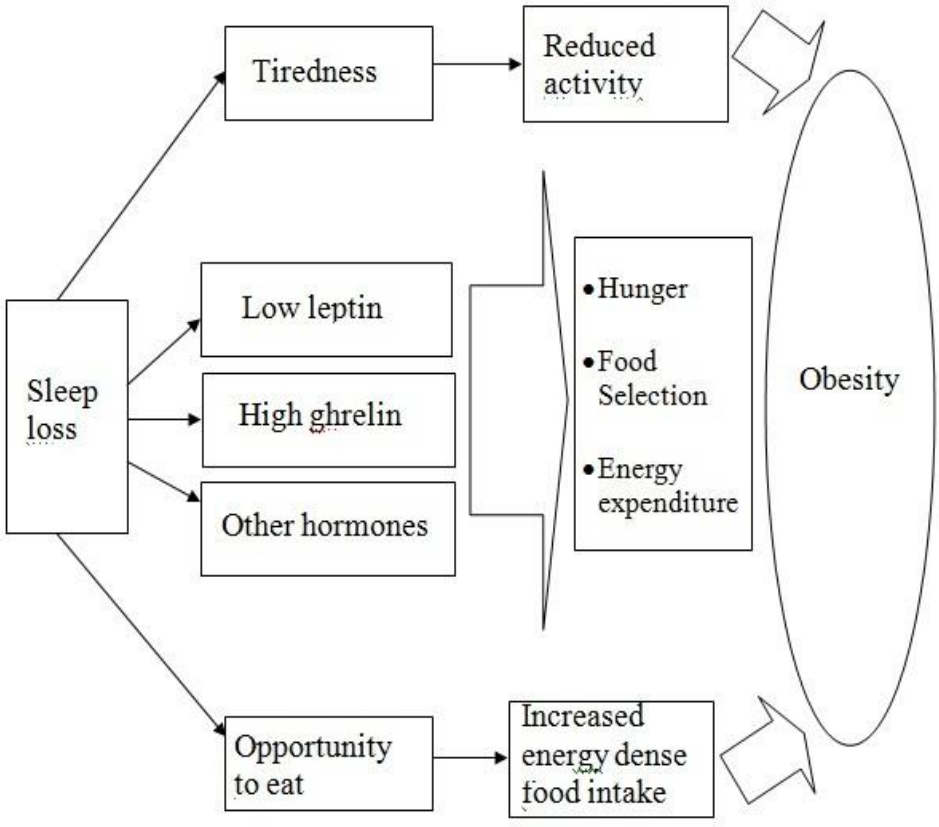

Figure 1-5. Potential mechanisms that short sleep duration may link with increased risk for obesity.[175]

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1.5.5.1 Sleep and regulation of appetite hormones

Alteration in activity of sympathetic nervous system may result in alterations in the release of appetite hormones such as leptin and ghrelin.

1.5.5.1.1 Leptin

Leptin, secreted primarily from fat cells (adipocytes), is a peptide hormone that promotes satiety, and has been found to play an important role in metabolism.[176] In energy deficit conditions, low leptin levels strongly signal energy deficit to the hypothalamus (the central homeostatic regulator), which would increase hunger and food intake (Figure 1-6).[176]

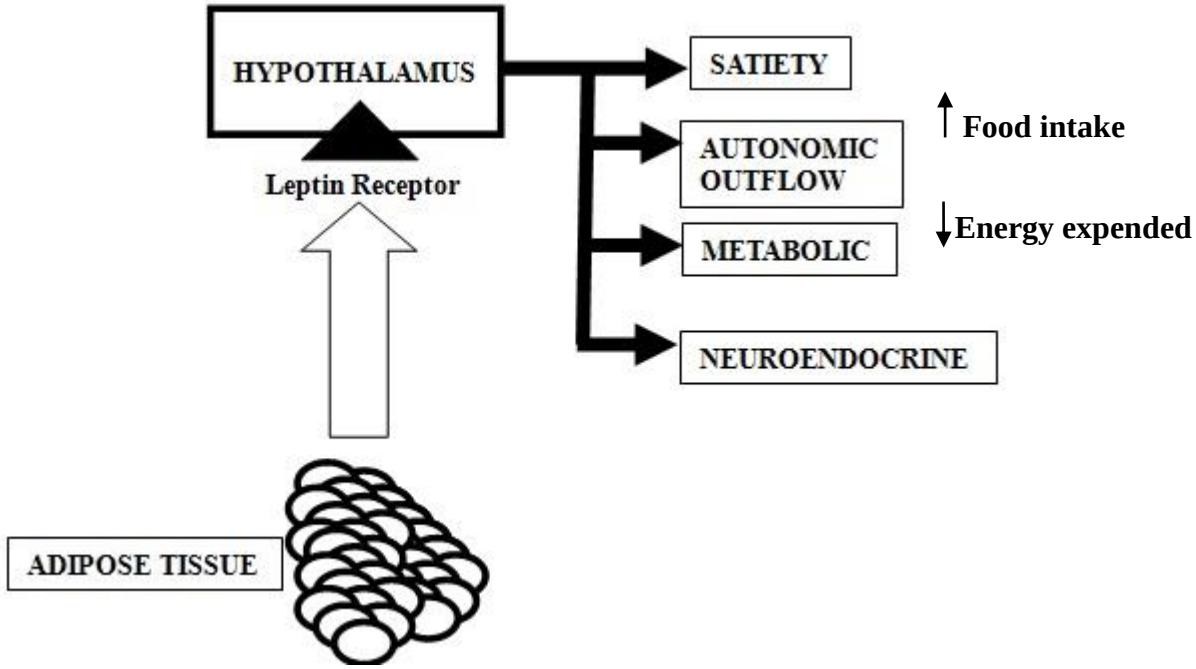

Figure 1-6. Effect of leptin on regulation of energy balance.[176]

Used with permission from Dr Taheri.

There are two groups of neurons within the hypothalamic arcuate nucleus (ARC) that are particularly influenced by leptin. The melanocyte stimulating hormone (MSH)/cocaine and amphetamine regulated transcript (CART) neurons mediate satiety.[177] These neurons are activated by leptin. Neuropeptide Y (NPY)/Agouti-related peptide (AGRP) neurons mediate appetite and their activity as well as peptide gene expression are reduced by leptin.[177] Obesity results in high leptin levels suggesting a state of leptin resistance. This may be because of reduction of leptin transport into the central nervous system (CNS). Thus, low leptin, signalling low fat stores, which has a potential to threaten reproductive function, is a much more powerful signal than high leptin levels.[176]

Evidence from early epidemiological[121, 123] and experimental studies suggested [178] that sleep loss is associated with reduced leptin levels. Taheri and colleagues[121] observed 15.5% lower leptin levels (p for slope = 0.008) in those with shorter sleep (5 hours vs. 8 hours) sleep in a large population study (n = 1,024). Spiegel and colleagues[179] studied 12 healthy men after 6 days of sleep restriction (total sleep duration was 4 hours per night), followed by 6 days with total sleep opportunity of 12 hours per night. The study was conducted under constant calorie provision. They found that 4 hours sleep was associated with a reduction in leptin levels by 18% (2.6 ng/mL vs. 2.1 ng/mL; p = 0.04) compared to 12 hours of sleep. The reduction in leptin observed by both the Taheri[121] and Spiegel[179] studies are equivalent to levels of leptin observed after significant calorie restriction (1000 kcal/day). With calorie restriction, as commonly practiced with various diet plans, leptin levels diminish, providing a strong energy deficit signal that subsequently promotes weight regain.[176]

In contrast, Omisade and colleagues[180] reported that sleep restriction was associated with an increase in leptin levels among 15 healthy women (aged 18-25 years). The participants' sleep duration and eating habits were monitored a week prior to the study. The change in leptin levels was assessed after two consecutive days: a) after a 10-hour sleep opportunity and b) after a night of sleep restriction with total sleep duration of 3 hours. Participants were asked to complete an appetite questionnaire on both days. The level of hungers was estimated using 10 cm scales (0 indicated "not all hungry" and 10 indicated "extremely" hungry). Morning leptin levels increased significantly after sleep restriction compared to baseline ($z = -1.98$, $p = 0.04$). While, hunger and increased appetite for high caloric density food did not significantly differ between these conditions using Wilcoxon Signed Ranks analyses. In a similar study, Pejovic and colleagues[181] assessed the effect of a 7-day sleep protocol (four nights of normal sleep, one night sleep restriction, and two nights of sleep recovery) among 21 overweight men and women, and they found that the plasma leptin levels significantly increased after one night sleep loss (mean difference of leptin levels, post deprivation minus baseline: 3.43 ± 0.89 (ng/mL), $p = 0.001$) and the mean plasma levels were non-significantly higher impact women compared to men (mean ± SD, 17.8 ± 4.3 (ng/mL) vs. 13.5 ± 2.5 (ng/mL), $p>0.05$). No significant change was observed in hunger and appetite levels. Results from an epidemiological study[182] also reported that leptin levels had a 7% (95% CI, 1.01 – 1.11) increase for every 1-hour decrease in total sleep time among 561 adults using PSG measured sleep in full adjusted model, controlling for potential confounders including: age, gender, ethnicity, waist circumference, apnoea hypopnoea index, hypertension, and diabetes. Moreover, the mean leptin level for short sleepers (<5.5 hours) was 50.4 ng/mL (95% CI, 42.2 -60.2, while it was 39.4

ng/mL (95% CI, 34.2 - 45.4) for long sleepers (>7 hours), compared to normal sleepers (7-8 hours).

Overall, based on the highlighted evidence, the relation between sleep duration and change in leptin levels is inconsistent, and may be due to differences in study design, patient population examined, degrees of adiposity, and the sleep restriction protocol. Importantly, leptin is a hormone that signals long-term energy deficit and is unlikely to change after very short sleep restriction. It is of note that the study by Taheri and colleagues found associations between leptin levels and habitual sleep rather than the sleep on the night before venepuncture.[121]

Only a small number of epidemiological and experimental studies have evaluated the association between sleep loss and change in leptin levels. Some of the factors that may be responsible for inconsistent findings from these studies is discussed in detail below.

In the study by Spiegel and colleagues,[179] sleep loss was chronic and partial (restriction of sleep to 4 hours for six days).[179] In contrast, Pejovic and colleagues[181] did not observe any change in leptin or cortisol level or evening levels of blood pressure/heart rate following one night of sleep loss. In the study by Spiegel and colleagues,[179] restricted sleep duration was found to be associated with reduced leptin levels after one week of sleep restriction and extension of bedtimes and their findings are in agreement with findings from two epidemiological studies, which reported that a reduction in leptin levels occurred with habitual (longer term) sleep, independent of BMI.[83, 85] Leptin signals long-term state of adipose stores and is more likely to be associated with longer term changes in sleep duration. Finally, results from studies[180,

[181]with female participants suggest that females have a significantly greater leptin response or the opposite response to men to sleep restriction compared to men.[183, 184] The observed sex differences is yet to be understood, however it is believed that women maybe more vulnerable to health risks from behavioural factors such as restricted sleep.

Overall, inference from experimental studies is limited, due to several factors including; their small sample size (<12 participants), quantity and duration of sleep deprivation, method of sleep deprivation, setting for the sleep deprivation (e.g. sleep laboratory), limited generalizability (many restricted to young healthy males), failure to control for or capture changes in calorie intake and energy expenditure within periods of experimental studies, and use of historical blood samples, which may have resulted in lack of difference in leptin levels between experimental conditions. It is also important to consider that cross-sectional design of epidemiological studies on association between sleep duration and leptin limits the ability to infer the temporal relationship between sleep duration and plasma leptin concentrations.

In general, the cross-sectional study design is a very efficient approach to evaluate a large number of people. There are also a few issues that need to be considered in evaluating cross-sectional studies. The main limitation is that the interpretation of causal association between exposure (e.g. sleep duration) and outcome (e.g. change in leptin levels) is impossible using a cross-sectional study design, because sleep duration and leptin levels are assessed simultaneously. Although, results from epidemiological studies[83, 85] showed that decreased sleep time was associated with decreased leptin, it is still impossible to make any conclusion, whether sleep loss can cause a decrease in

serum leptin concentrations. The other major issue is that sample in a cross-sectional study may not be a representative of the population, and the results of the study may differ if another time frame has been chosen.

Cross-sectional design is susceptible to bias due to low response and misclassification due to recall bias. The other limitation is that a cross-sectional study is more appropriate to evaluate prevalent rather than incident outcomes, as the population from which the subjects are drawn would be unclear. Lack of knowledge of the actual population means that the cases and exposure cannot be certain. Whereas, population is defined in cohort and the number of the subjects that are exposed or have the disease is certain, thus incident can be calculated.

1.5.5.1.2 Ghrelin

Ghrelin is a gastric hormone that signals hunger acutely to the hypothalamus, and over time, promotes adiposity.[185] Ghrelin has opposing actions to leptin on hypothalamic neurons.[185] Taheri and colleagues,[121] in their population study, found that short PSG-measured sleep (sleep duration<5 hours) predicted 14.9% higher ghrelin levels compared to sleeping of 8 hours per night. Recently, Hogenkamp and colleagues[186] in a randomised cross-over study, assessed the effect of two conditions (8 hours of sleep vs. 24-hour total sleep deprivation) and they found that in the morning of total sleep deprivation, the plasma ghrelin levels were 13% higher ($p = 0.04$) and sleep-deprived individuals tended to choose larger portion sizes for all food items (kcal mean ± SD, 8 hours of sleep 359 ± 31 vs. 400 ± 36 total sleep deprivation, $p<0.05$). Sleep-deprived participants also chose larger portion of snacks after breakfast (310 ± 29 vs. 337 ± 30,

$p<0.05$ respectively). No difference was observed in food selection between the two conditions.

In a similar study,[187] nine healthy men were examined under three different conditions; a) one night with total sleep time of 7 hours, b) one night with total sleep time of 4.5 hours, and c) one night with total sleep deprivation. Participants were asked to score their hunger from scale of 0 (not at all) to 9 (extremely). The findings showed that hunger rates (3.9 ± 0.7, 2.2 ± 0.5 vs. 1.7 ± 0.3; $p<0.05$) and plasma ghrelin levels (0.85 ± 0.06 ng/mL, 0.77 ± 0.04 ng/mL vs. 0.72 ± 0.04 ng/mL, $p<0.05$) were significantly higher after total sleep deprivation compared to 7 hours sleep or 4.5 hours sleep conditions. No changes were observed in serum leptin levels across the three conditions.

In a study involving 10 overweight healthy men under calorie restriction, Nedeltcheva and colleagues[188] observed an increase in ghrelin levels (mean (SD), 75 (40) ng/L vs. 84 (47) ng/L) but no change was detected in leptin levels between two conditions of seven nights of sleep restriction (5.5 hours sleep per night) followed by seven night sleep recovery (8.5 hours sleep per night).

Evidence on the association between sleep duration and ghrelin is relatively consistent. Only, the result of a recent experimental study[189] showed that there was no association between sleep duration and ghrelin and leptin levels. The study was relatively small ($n = 12$) and the participants were lean (mean body max index = 22.3 kg/m^2) and no calorie restriction was applied.

1.5.5.2 Sleep and food intake

The selection of unhealthy foods and shifting toward foods that quickly release their energy is another potential consequence of sleep deprivation. It has been previously reported that individual's appetite ratings on the 10-cm visual analogue scale for high carbohydrate content foods (sweet, salty, and starchy) increased between 33% to 45% after sleep restriction.[190] Brondel and colleagues[189] assessed alterations in energy intake after acute partial sleep restriction among 12 men (mean age (SD): 22 (3) years, mean BMI: 22.30 (1.83) kg/m^2) under ad libitum diet. The findings showed that participants consumed higher energy (mean± SD, kcal 559 ± 617 (i.e. 22%) $p<0.01$) after sleep restriction compared to 8 hours sleep session. In a randomised cross-over study, Nedeltcheva and colleagues[188] examined whether sleep restriction could reduce the effect of a low-calorie diet among 10 overweight participants (mean age (SD): 41 (5) years, mean BMI (SD): 27.4 (2.0) kg/m^2) over 14 days with either 8.5 hours or 5.5 hours sleep. During 14 days, individuals consumed their same dietary pattern with calorie restriction up to 90% of their resting metabolic rate at baseline. Total individualised calorie was divided among breakfast (25%, 8:00 – 9:00 am), lunch (30%, 12:30 – 1.30 pm), dinner (35% 6:30 - 7:30 pm), and snacking (10%, 9:00 pm). In order to determine the actual consumption, the food was weighted before each meal. Participants were asked to determine their level of hunger using a 10-cm visual analogue scale, before each meal and at 11:00 pm. Findings showed that approximately half of the weight loss occurred during the 8.5 hours sleep, while only 25% of the weight loss occurred during 5.5 hours sleep condition (Mean (SD) reduction in fat loss (kg) 8.5 hours vs. 5.5 hours sleep: 1.4 (0.9) vs. 0.6 (0.6) kg, $p = 0.043$). Moreover, sleep deprived individuals tending to snack particularly during night, when food intake

preferences normally decrease during evenings such increased vulnerability to overeating could potentially promote weight gain.[188] Energy needs were also found to be increased following sleep restriction,[191] and sleep deprived individuals may potentially tend to compromise this energy need by selecting foods that quickly release their energy. However, higher intake of some nutrients such as carbohydrates may exceed the energy needed and promote weight gain.

1.5.5.3 Sleep and energy expenditure

Energy expenditure is another possible underlying mechanism mediating the interaction between sleep and obesity. Excessive daytime sleepiness and fatigue as a result of insufficient sleep may potentially limit levels of physical activity and increase the probability of engaging in sedentary behaviours such as sitting and watching TV.[128, 192]

It has been previously reported that the impact of disrupted sleep on daily physical activity is even higher among younger age groups.[193] In a large population-based study, Ortega and colleagues[192] assessed the sleep patterns of 2,179 (1,139 females) Spanish adolescents (ages ranged from 13 to 18.5 years) and also examined the association between sleep duration and morning tiredness. Findings showed that female participants who slept 8 hours or longer were less likely to report morning tiredness (OR 0.49, 95% CI 0.34 – 0.71), but no association was found among male participants (OR 0.87, 95% CI 0.58 – 1.31). Additionally, sleeping less than 8 hours was associated with lower probability of engaging in any physical activities (OR 0.64, 95% CI 0.45 – 0.93) and higher probability of excessive hours of watching TV (≥3 hours per day) (OR 2.15, 95% CI 1.42 – 3.27) in males only. Results of a similar study

in a sample of 383 adolescents (aged 11 to 16 years) showed that each hour reduction in total sleep time was associated with 80% increased risk for obesity (95% CI 0.11 – 0.34). Additionally, sleep disturbance was significantly (Regression coefficient β = -7.48, p = 0.001) associated with decreased physical activity levels among these individuals.[128]

On the other hand, findings from experimental studies[188, 194, 195] have been relatively controversial. Nedeltcheva and colleagues[188] found no significant difference in total energy expenditure of their 10 overweight participants under two sleep conditions, (2136 (342) vs. 2139 (393) kcal/day, 8.5 hours vs. 5.5 hours respectively). In another study, Jung and colleagues[194] found that energy expenditure during 40 hours of sleep deprivation significantly increased by 7% compared to 24 hours normal sleep (total sleep time was 8 hours (approximately 134 ± 2.1 vs. 228 ± 23 kcal) among 7 healthy volunteers. Benedict and colleagues[195] in a crossover design examined 14 healthy men during a 24-hour consecutive sleep restriction followed by sleep recovery and found that energy expenditure, was significantly reduced by approximately 20% after acute sleep loss (mean (SD) kJ/min, 1.06 ± 0.06 vs. 1.32 ±6 0.07 kJ/min; $p<0.0001$). There are several reasons for discrepancies in the findings from experimental studies including variations in protocol such as duration of sleep restriction and participant characteristics. There is a need to study the impact of sleep restriction under more realistic conditions.

The exact mechanism underlying any associations between sleep loss and energy expenditure are largely unknown. It has been consistently reported that sleep loss is associated with a decrease in leptin levels, which could explain a reduction in energy

expenditure following sleep loss. Moreover, sleep restriction also found to be associated with an increase in ghrelin levels, which are associated with lower levels of resting and energy expenditure.[194] Sleep has an important role in thermoregulation. Body temperature reduces during sleep suggesting energy dissipation. Sleep restriction may affect this reduction in body temperature, thus avoiding energy dissipation. This could contribute to weight gain. This hypothesis, however, has not been examined.

1.5.5.4 Sleep and circadian disruption

Disruption in sleep-wake cycle and sleep patterns similar to those observed among shift-workers is another possible hypothesis that can explain how sleep may be linked to obesity.[196] As previously described, circadian rhythms are controlled by the central circadian pacemaker, which is located in the suprachiasmatic nucleus in the hypothalamus. Physiological functions within cells are synchronised by the central oscillator. In a recent experimental study, Scheer and colleagues[197] studied 10 adults (5 female) under a 10-day laboratory protocol, which participants ate and slept through the entire circadian cycle followed by 28 hours of total wakefulness. Findings showed that circadian misalignment was associated with decreased leptin level (−17%, $p < 0.001$), increased glucose (+6%, $p < 0.001$), increased mean arterial blood pressure (+3%, $p = 0.001$), and reversed daily cortisol rhythm. It has been previously shown that sleep restriction was associated with a decline in the diurnal amplitude of leptin. Spiegel and colleagues[178] evaluated 11 subjects (mean age (SD), 22 (1) years; mean BMI (SD), 23.4 ± 0.5 kg/m^2) under different bed conditions (three nights with total sleep duration of 8 hours, six nights with total sleep duration of 4 hours and seven nights with total sleep duration of 12 hours). The findings showed that rhythm

amplitude of leptin significantly decreased during sleep restriction compared to sleep extension (-19%, -26%, and -20%, respectively). Their results also indicated there was an alteration between the pattern of regulation of leptin and cortisol in the 24-hour, following the sleep restriction with declining leptin levels significantly associated with elevation of cortisol levels at the beginning of the sleep time.

The disruption in body's internal clock may also disrupt metabolic mechanisms in different cells, tissues and organs of the body and alteration in regulation of several nutrients (e.g. glucose, fatty acids and triglycerides) and hormones (e.g. leptin, ghrelin, and insulin) may also influence appetite, satiety, and also modify food intake.[178, 198-200]

1.6 Aims of thesis

The growth in the prevalence of overweight and obesity is a major challenge for public health worldwide.[70] Obesity is an important risk factor for several adverse health outcomes including; diabetes, hypertension, cardiovascular disease, several cancers, and mental health problems.[201] It is also known that there is a close link between obesity and obstructive sleep apnoea (OSA).[105] To date, a substantial number of studies have investigated the various determinants that are potentially associated with an increased risk of obesity.[202] Clearly energy imbalance is the cause of overweight/obesity, therefore the majority of health interventions, designed to tackle obesity have targeted directly the energy balance equation, concentrating on diet and physical activity. Unfortunately, despite concerted efforts to tackle obesity in this way, limited success has been achieved.[202] Therefore, a greater understanding of factors that alter diet and physical activity is needed. Emerging evidence suggests that the contribution of factors such as sleep quantity and quality to obesity need to be studied in more detail as sleep disturbance could contribute to alterations in the energy balance equation. In recent years, the important potential role of sleep duration in the promotion of obesity has been identified by numerous epidemiological studies.[114] Thus, identifying the determinants of factors that drive short and long sleep duration may be beneficial for designing approaches to obesity prevention and treatment.

The focus of this thesis is to investigate the association between sleep and obesity, and its impact on health and wellbeing. The detailed hypotheses and the approach to assess such hypotheses for each chapter are discussed below:

Chapter 2: Based on evidence provided earlier, there is a positive link between sleep duration and increased risk for obesity. However, the majority of studies have been among younger or middle-aged individuals and it is not known whether sleep and obesity are significantly associated among older individuals who are at greater risk of chronic disorders such as diabetes. Sleep patterns may dramatically change across the life span; therefore the sleep duration may not be associated with alteration in metabolism and development of chronic diseases such as obesity among these individuals. It is also hypothesised that gender may also have an impact on association between sleep duration and obesity, but there is a gap in current knowledge for drawing any confirmative conclusion in this matter.

The focus of this chapter is on evaluating factors that are associated with both short and long sleep duration among 10,088 older Chinese individuals. It is hypothesised that demographic, socio-economic, health behaviours and medical condition variables may be associated with sleep duration among these individuals. I also investigated the cross-sectional associations between sleep duration and chronic conditions including obesity, hypertension, and diabetes following adjustment for potential confounders are assessed.

Chapter 3: It is believed that sleep quality as well as sleep quantity may increase the risk for obesity. It is hypothesised that poor sleep quality has a negative impact on mood and quality of life among individuals with extreme obesity. In this chapter, I investigated the cross-sectional associations among sleep disturbance, quality of life, anxiety and depression in 270 patients with extreme obesity attending a specialist weight management service in the UK.

Chapter 4: There is a close link between obstructive sleep apnoea (OSA) and obesity. Excessive daytime sleepiness is a well-known feature of OSA and may worsen the obesity per se. Early treatment of OSA may prevent its further adverse health complications. Evidence on effectiveness of lifestyle interventions as treatment approaches for OSA has not been systematically reviewed. In this chapter, it is hypothesised that lifestyle modification strategies and weight loss through the application of diet and exercise or their combination may be effective for the treatment of OSA. A systematic review and meta-analysis approach was conducted to examine the above hypothesis.

2 PREDICTORS OF TOTAL SLEEP DURATION IN OLDER CHINESE ADULTS- THE GUANGZHOU BIOBANK COHORT STUDY (GBCS)

2.1 Abstract

Introduction: It has been reported that both short and long sleep duration are associated with an increased risk for multiple adverse health outcomes and even mortality. The mechanisms underlying these associations remain unknown. The present study explored the potential socio-demographic, socio-economic, and medical condition variables associated with short and long sleep duration and also examined whether sleep duration is associated with the common chronic disorders of obesity, hypertension, and diabetes mellitus.

Methods: Participants (n = 10,088) were of Chinese origin and aged ≥50 years. Logistic regression was used to estimate the strength of associations of potential factors linked to short and long sleep duration.

Results: In males, sleep duration of 6-<7 hours and ≥9 hours were inversely associated with increased risk of obesity (6-<7 hours: Odds Ratio (OR) 0.61, 95% CI 0.38 – 0.99, ≥9 hours: OR 0.51, 95% CI 0.28 – 0.91, respectively). In females, sleep duration of ≥9 hours was positively associated with obesity (OR 1.45, 95% CI 1.16 – 1.80). Additionally, sleep duration of 6-<7 hours was associated with increased risk of hypertension among males (OR 1.55, 95% CI .105 – 2.29), while in females, sleep duration of 8-<9 hours was associated with hypertension (OR 1.19, 95% CI 1.01 –

1.41). Females, who reported sleeping 6-<7 hours per night were more likely to have diabetes compared to those reported 7-<8 hours (OR 1.55, 95% CI 1.07 – 2.25).

Conclusion: This study showed that short sleep duration was associated with female gender, older age, being widowed, and having lower education and income levels, and that long sleep duration was associated with hypertension. Understanding factors that are associated with both short and long sleep duration may inform the design of interventions aiming to improve sleep. This, in turn, allows us to test the hypothesis of whether altering sleep duration can have an impact on health. The gender differences in factors associated with both short and long sleep duration require further exploration.

2.2 Introduction

The role of sleep in health and wellbeing is increasingly appreciated.[3] A group that is particularly vulnerable to sleep problems is the older population who also carry an increasing burden of chronic disorders.[21] There is increasing evidence that extremes of sleep duration are associated with adverse health outcomes. This is supported by detailed study of putative mechanisms within sleep laboratories.[190] If sleep is indeed an important lifestyle factor that contributes to various aspects of health and wellbeing, then improving sleep could have beneficial effects, particularly in vulnerable groups such as the older population.[21]

As previously stated in *Chapter 1*, sleep patterns change significantly across the lifespan. In general, evidence suggests that older people sleep less and may experience fragmented sleep compared to younger people.[21] The decline in sleep continuity may negatively influence mood, cognition and overall functioning.[203] It was previously reported that approximately half of individuals over the age of 65 years suffer from at least one sleep problem, and in particular insomnia.[204] Data from epidemiological studies conducted in Western countries suggest that the prevalence of insomnia ranges between 6% and 10%.[204, 205]

There is a lack of data on sleep habits and the prevalence of insomnia among older Chinese people. Two previous epidemiological studies conducted in Hong Kong[206] and Taiwan[207] reported a diverse estimate of insomnia prevalence (38.2% vs. 6%). A recent epidemiological study[208] assessed the prevalence of insomnia among 5,001 Chinese living in mainland China aged ≥18 years. The authors found that insomnia affected 39.4% of the participants and that the prevalence was slightly higher among

older and socio-economically deprived individuals. They also found that non-employed groups and housewives had the highest rates of insomnia (≥43.7%).[208] The observed difference in prevalence of insomnia among Hong Kong, Taiwan, and mainland of China inhabitants may be explained by difference in social and socio-economic factors, and healthcare assessment and delivery across these regions.

The mechanisms underlying the onset and development of sleep problems among older people are not fully understood but are likely to be a combination of ageing itself combined with other biological and/or psychosocial factors.[209] Retirement from work is normally associated with reduced daily activity, which may cause irregular schedules of sleeping and increased napping. Chronic health conditions such as cardiovascular disease, diabetes, chest diseases, arthritis, and the menopause are also prevalent among older people and may further disrupt sleep.[209] Moreover, major life events such as the death of a spouse, financial strain, reduced coping skills, reduced cognitive function, disability, and medication side effects may also contribute to sleep disturbance.[63] Sleep may also be disrupted as a result of poor lifestyle including lack of physical activity, smoking, excessive alcohol consumption, and napping.[63, 210] Social and cultural factors may also contribute to poor sleep among older individuals.[211] Evidence from numerous epidemiological studies in the United States has also confirmed the impact of ethnicity on sleep duration, sleep complaints and other sleep problems among older individuals.[21, 209] In some cultures, including Mediterranean, Chinese and South American countries, afternoon napping (siesta) is a traditional practice. In China, it is widely accepted among all Chinese, particularly in older Chinese, that afternoon napping is a robust activity and can improve the health

of older people. The effect of napping on health has yet to be confirmed; however it was previously reported that sleeping during the day "siesta" may increase the risk of cardiovascular morbidity and mortality. Results from analysis of prospective data 445 older residents (mean age: 70 years) of Jerusalem, Israel showed that total mortality rate (20% vs. 11%, p = 0.001) of those who practiced the siesta was significantly higher compared to those who did not. In a full-adjusted for potential confounders, the siesta remained as a strong predictor of total mortality (OR 2.1, 95% CI 1.1 – 3.9).[212] Findings from a recent large population-based study[213] among 3,079 Taiwanese aged 64 years and older showed that compared to individuals with night-time sleep only, those older individuals who reported taking a nap during the day, regardless of duration of nap, did not have any differences in mortality risk. However, a recent study from the Guangzhou Biobank Cohort Study (GBCS) showed that frequency of daytime napping was significantly associated with increased risk of type 2 diabetes, among 19,567 older Chinese men and women (OR 1.28, 95% CI 1.15 – 1.44).[214]

Understanding factors that correlate with both short and long sleep duration may be beneficial for designing health interventions to address and modify those factors in order to improve sleep and eventually prevent further health complications. For example, Sherrill and colleagues[215] investigated the impact of moderate physical activity on sleep problems among 722 adult men and women participants and they found that regular activity at least once a week was associated with a lower risk for difficulties maintaining sleep (OR 0.71, 95% CI 0.50 – 0.99) and also for any other sleep problem (OR 0.62, 95% CI 0.44 – 0.87). In another study, Merill and colleagues[216] assessed whether an intensive lifestyle modification programme (diet

and physical activity) can reduce sleep problems among 2,624 individuals aged 30 to 80 years. The findings showed that from baseline to end of four-week programme the percentage of people with insomnia significantly reduced by 64%. Thus, it is possible to improve sleep through specific interventions with potential downstream health benefits. Studying sleep patterns in a well-established and well-characterised cohort can help identify modifiable factors that are associated with both short and long sleep duration, which can inform the development of future interventions. The aim of the work in this chapter was to examine factors associated with sleep duration among the older Chinese and also determine the role of sleep in common and emerging chronic disorders including obesity, hypertension, and diabetes mellitus.

2.2.1 The impact of sleep on health

Sleep is a normal and restful condition for both brain and body, in which the awareness and body movement decreases. On average, a third of adult life is spent sleeping. Acquiring sufficient sleep is recognised as an important part of a healthy lifestyle as well as diet and physical activity. The impact of sleep on health and well-being has been a main interest of numerous studies. Kripke and colleagues[3] found that a sleep duration of 7 to 8 hours was associated with lowest risk of mortality among 636,095 women, aged 30 to 102 years old (Figure 2-1). It has been found that deviation from this range of sleep may be associated with adverse health outcomes such as obesity, cardiovascular disease, diabetes, and even death.

Recently, Cappuccio and colleagues[217] systematically reviewed prospective population-based studies and quantified the impact of short and long sleep duration on all-cause mortality. The authors identified 17 studies, which represented

1,382,999 individuals from eight different countries. Self-reported sleep measures (i.e. self-reported questionnaire), rather than objective measures (i.e. actigraphy, polysomnography), were used across all the studies. The pooled analysis demonstrated that compared to sleep duration of 7 to 8 hours, hazard ratio for all-cause mortality for short sleep duration (<5 hours sleep per night) and long sleep duration (≥8 hours sleep per night) was 1.12 (95% CI, 1.06 - 1.18) and 1.30 (95% CI, 1.22 - 1.38), respectively. The link between sleep and mortality is yet to be understood fully and requires further investigations. Some mechanisms for this relationship have been proposed and are discussed in the thesis. There are several interrelated aspects of sleep including sleep duration and quality that need to be considered when studying the impact of sleep on health. Increasing evidence highlights the importance of sleep quality as well as quantity for optimal health.[4] It is believed that the potential adverse physiological outcomes of shorter and or poor quality sleep such as obesity, diabetes, and cardiovascular may mediate the pathways between sleep and mortality.[4] Despite these hypotheses, it is important to note that there are no data examining the relationship between mortality and objective sleep measures (i.e. actigraphy, polysomnography).

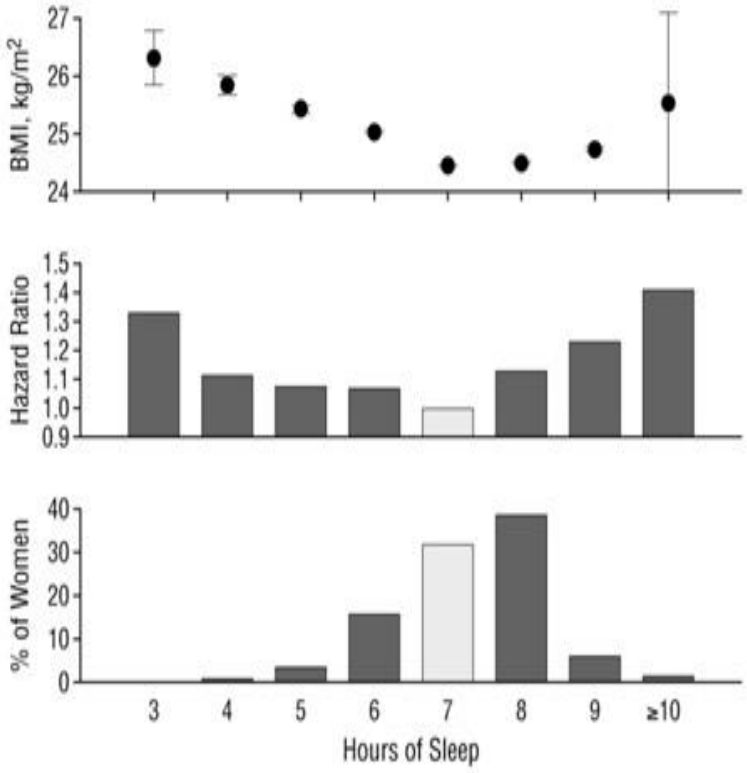

Figure 2-1. The average BMI and hazard ratios for mortality according to self-reported sleep duration among 636,095 women[3], The hazard ratios (95% CI) for 3 hours of sleep and 10 hours of sleep are 2.05 (1.68 – 2.50) and 2.14 (2.04 – 2.28), compared to 7 hours of sleep respectively.

Used with permission from Professor Daniel Kripke.

2.2.2 Physiological consequences of sleep loss

Evidence indicates that sleep loss is associated with alterations in metabolic and endocrine function.[218] Sleep plays an important role in regulation of body temperature; therefore sleep loss is associated with absence of nocturnal drop in body temperature and inability to dissipate body heat.[219] This may result in energy retention that could, over a prolonged period, predispose to obesity. It was previously found that sleep restriction may result in activation of the sympathetic nervous system and may also

alter the activity of the hypothalamic-pituitary-adrenal axis which leads to higher secretion of cortisol (stress hormone) levels.[44]

Sleep loss appears to influence circulating appetite hormones (leptin and ghrelin) in a direction, which could result in higher calorie intake and lower energy expenditure, eventually resulting in excessive weight gain and obesity.[187, 190] It has also been found that sleep curtailment is associated with an increase in cortisol secretion, impaired glycaemic control, and impaired growth hormone secretion.[220] It is known that thyroid hormones are an important regulator of carbohydrate metabolism, oxygen consumption, and cardiac output.[221] Alterations in regulation of thyroid-stimulating hormones as a result of sleep loss may result in the development of glucose dysregulation and insulin resistance and predispose to diabetes in the longer term.[221] Thus, hormonal changes with sleep deprivation are likely to be key to adverse metabolic outcomes and obesity.

Findings of epidemiological studies that previously explored the possible link between sleep duration, obesity, hypertension and diabetes are fully discussed in *Chapter 1.* A summary of methodological limitations of these studies is discussed as below.

2.2.2.1 A summary of methodological limitations of previous studies that assessed the link between sleep duration, obesity, hypertension and diabetes

In sum, a large body of evidence provides strong support for associations between sleep duration, obesity, hypertension, and diabetes. However, the underlying mechanisms for such associations are yet to be fully understood. It is very important to note the limitations of pervious work, in order to inform future research. The two key methodological limitations of previous studies are the reliance upon cross-

sectional studies to support a link between sleep and risk of obesity, hypertension and diabetes, and the almost exclusive reliance on self-report measure of sleep. Although longitudinal associations between sleep and these adverse health outcomes have been previously assessed by several large epidemiological studies, it is still unknown, whether short sleep duration, or long sleep duration or both cause any of these adverse health outcomes. Evidently, future experimental and intervention studies are needed to carefully manipulate sleep length for effective treatment purposes. Moreover, objective measures of sleep such as actigraphy and polysomnography are needed to strengthen the validity and reliability of previous findings. Beyond these two key limitations, it is also important to note some inconsistencies across studies. Only a few studies assessed the impact of gender on associations between sleep duration, obesity, and hypertension and the findings were inconsistent. Furthermore, few studies have suggested that the positive association between sleep duration, obesity, hypertension and hypertension, which were observed among younger individuals, are not present among older individuals. The above noted limitations and inconsistencies suggest that there is a need to think critically about design of future work, including consideration of key factors that may influence study findings.

2.2.3 Psychosocial consequences of sleep loss

The pivotal role of sleep in the relationships among extreme obesity, and mood and quality of life are discussed in *Chapter 3*. It is known that sleep loss may also have adverse effects on mental health. Chronic sleep deprivation could potentially result in anxiety, distress, depression and excessive alcohol use among adults.[222] A meta-analysis including 19 studies[222] investigated the impact of sleep loss on performance,

and showed that the adverse effect of sleep loss on mood was much higher compared to cognitive and motor performance. Sleep loss may also have deleterious effects on several cognitive tasks such as concentration, attention and vigilance.[223] Moreover, insufficient sleep has previously been found to be associated with significant impairment in a variety of tasks that need higher cognitive processes including complex decision making, problem solving, and inhibitory control.[223] It is believed that adverse consequences of prolonged wakefulness on the prefrontal cortex may mediate the casual pathways between sleep loss and impairment in those tasks.[224] Evidence suggests that the prefrontal cortex is relatively sensitive to the effects of prolonged of wakefulness that occurs with chronic sleep loss.[225] Lack of sufficient sleep can cause a decline in neural processes within the prefrontal cortex;[224] therefore there is a cumulative need for other brain regions to compensate for these deficits.[224] It was previously found that even sleep loss for one or two nights could result in decrements in cognitive performance of tasks requiring involvement of the prefrontal region.[226] It has been found recently that there is a positive link between sleep deprivation and deficits in moral judgment, reaction to frustration, emotional decision making, and mood regulation.[223] It could be interpreted that adverse effects of sleep loss are not only limited to cognitive abilities but may also negatively influence personality and social interaction.

2.2.4 Consequences of long sleep duration

The majority of studies have placed greatest emphasis on short sleep duration, and mainly on insomnia. Therefore, the consequences of sleeping longer than average is less well understood.[227] PSG sleep data have shown that long sleepers have shorter

SWS, while they have prolonged wakefulness and REM sleep compared to normal sleepers.[228] As stated earlier, there is a U-shaped association between sleep duration and mortality,[217] which highlights sleeping longer than the average amount may potentially increase the risk for death. The causal role and mechanisms of long sleep duration in mortality is yet to be understood. The possible link between long sleep duration and mortality can be explained by the fact that prolonged sleep is associated with increased sleep fragmentation which could potentially have a negative impact on overall health and well-being.[229] The other possible explanation is that long sleepers feel sleepy and lack energy; this could dramatically reduce stress tolerance and increase susceptibility of disease.[227] Finally, it has been hypothesised that lack of day light exposure (short photoperiod) due to extended time in bed could increase the risk for mortality in long run.[227]

2.2.5 Rationale for assessment of factors associated with short and long duration among older individuals

Both adverse physiological and psychosocial consequences as a result of deviation from recommended and average sleep duration (7 to 8 hours per night) have been observed. It has been previously found that demographic, socio-economic background and medical conditions may have an impact on sleep duration. For example, Kruger and colleagues[63] investigated factors that contributed to short and long sleep duration among 110,441 American men and women. They reported that both short and long sleep duration were associated with black ethnicity (≤5 hours vs. 7 hours: OR 1.39, 95% CI 1.84 – 2.17, and ≥9 hours vs. 7 hours: OR 1.72, 95% CI 1.59 – 1.87), lower income levels (≤5 hours vs. 7 hours: OR 0.91, 95% CI 0.87 – 0.95, and 8 hours vs. 7

hours: OR 0.96, 95% CI 0.93 – 0.98), current smoking (≤5 hours vs. 7 hours: OR 1.46, 95% CI 1.34 – 1.59, and ≥9 hours vs. 7 hours: OR 1.32, 95% CI 1.20 -1.45), depressive symptoms (5 hours vs. 7 hours: OR 1.23, 95% CI 1.18 – 1.27, ≥9 hours vs. 7 hours: OR 1.30, 95% CI 1.25 – 1.35), diabetes (≤5 hours vs. 7 hours: OR 1.19, 95% CI 1.07 – 1.33, ≥9 hours vs. 7 hours: OR 1.25, 95% CI 1.13 – 1.38), and heart disease (≤5 hours vs. 7 hours: OR 1.24, 95% CI 1.16 – 1.33, ≥9 hours vs. 7 hours: OR 1.11, 95% CI 1.03 – 1.19). They also observed that having long working hours (≥41 hours per week) (OR 1.52, 95% CI 1.34 – 1.72), obesity (OR 1.39, 95% CI 1.29 – 1.51) were strongly associated of short sleep duration. In Australia, Magee and colleagues[210] examined the sleep patterns in a sample of 49,405 adults aged 45 to 65 years. Their results indicated that short sleep is prevalent in this population. Moreover, sleep duration was associated with poorer self-rated health (<6 hours vs. 7 hours: OR 3.02, 95% CI 2.56 – 3.66, 6 vs. 7 hours: OR 1.68, 95% CI 1.51 – 1.88, ≥9 vs. 7 hours: OR 2.11, 95% CI 1.90 – 2.34) lower income levels (<6 hours vs. 7 hours: OR 1.74, 95% CI 1.48 - 2.04, 8 hours vs. 7 hours: OR 1.49, 95% CI 1.39 - 1.59, ≥9 vs. 7 hours: OR 3.0, 95% CI 2.79 - 3.37), being single (<6 hours vs. 7 hours: OR 1.27, 95% CI 1.13 - 1.44, 6 hours vs. 7 hours OR 1.24, 95% CI 1.16 - 1.33), current cigarette smoking (<6 hours vs. 7 hours: OR 1.58, 95% 1.34 - 1.86, 6 hours vs. 7 hours: OR 1.53, 95% CI 1.38 - 1.70) alcohol consumption (<6 hours vs. 7 hours: OR 1.26, 95% CI 1.06 - 1.49, ≥9 vs. 7 hours: OR 1.72, 95% CI 1.57 - 1.89), and obesity (<6 hours vs. 7 hours: OR 1.2, 95% CI 1.05 - 1.40, 6 hours vs. 7 hours OR 1.29, 95% CI 1.19 - 1.41). Similarly, the results of a recent study of 4,411 Korean adults aged 19 years and older, demonstrated that socio-economic characteristics, lifestyle factors such as smoking, and health-related characteristics, such as depression, are associated with short sleep

duration. Socio-economic characteristics and depression are also shown to be associated with long sleep duration.[230]

Previous studies have found a positive association between sleep duration and chronic disorders including hypertension, obesity, and diabetes. The majority of these studies looked at such associations in both men and women; some investigated the effect of gender and specific age group and observed different results. For example, Fang and colleagues[33] found that the probability of hypertension for those men (45-64 years) who slept <6 hours was higher compared to those who slept 8 hours (OR 1.29, 95% CI 1.05 – 1.60). In middle-aged women (45 to 65 years), the risk of hypertension was higher among those who slept >9 hours (OR 1.45, 95% CI 1.06 – 1.98). In another study, Lopez-Garcia and colleagues[40] could not observe any significant association between sleep duration and incidence of hypertension among older individuals (≥60 years). Tuomilehto and colleagues[50] found that there was a U-shaped association between sleep duration and type 2 diabetes among women (≤6 hours vs. 7 hours: OR 2.55, 95% CI 1.21 – 5.35, ≥8 hours vs. 7 hours: OR 1.76, 95% CI 1.12 – 2.61), but the observed trend among men was not statistically significant.

Data on sleep patterns of older Chinese are relatively sparse. Understanding factors that contribute to either short or long sleep duration or also understanding the impact of gender and age on such association may help the design of future interventions to improve sleep. These interventions can then be employed in studies to examine whether altering sleep can have an impact on health.

2.3 Aim and study questions

The purpose of the present study was to examine the sleep pattern of 10,088 older Chinese adults aged ≥50 years and examine a potential link between several factors (including demographic, socioeconomic, lifestyle and medical conditions), and sleep duration. Additionally, the potential association between sleep duration and hypertension, obesity and diabetes and the impact of gender and age was investigated.

The study questions included:

- What percentage of the participants of the study reported sleeping less or more than the average recommended sleep (7 to 8 hours)?
- What factors are associated with short or long sleep duration among older Chinese people?
- Is there any association between sleep duration and hypertension, obesity and diabetes among these individuals?
- Is there any difference between gender and also age group on association between sleep duration and hypertension, obesity and diabetes?

2.4 Methods

2.4.1 Study design

Details of the methods of the Guangzhou Biobank Cohort Study (GBCS), including sample characteristics and recruitment techniques have been published elsewhere.[231] In summary, the GBCS is a large population-based study, which started in October 2003, in joint collaboration between the Guangzhou Number 12 People's Hospital, University of Hong Kong, and University of Birmingham, that recruited older (≥50 years) residents in Guangzhou, which is the provincial capital of Guangdong province in Southern part of China and is one the most economically developed regions of China (Figure 2-2).

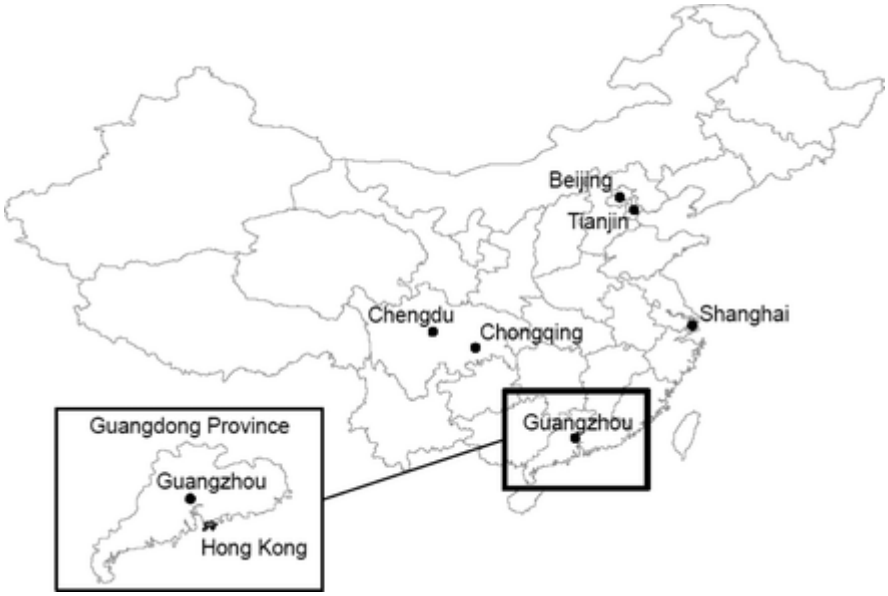

Figure 2-2. Geographical location of major urban areas in China (Approximate populations was 10 million in 2000).

The main objective of the study was identifying determinants such as genetic, lifestyle, occupational and environmental factors associated with chronic diseases. Participants were selected from a local social community centre named “Guangzhou Zunlao Xiehui” (“Guangzhou Health and Happiness Association for the Respectable Elders”). This is a very large non-governmental organization with open membership to anyone age 50 years or older for a minimal monthly membership of 4 yuan (1 USD = 8 yuan) with many branches throughout Guangzhou. After 18 months from initial recruitment of the first 11,000 participants, a pilot follow-up study achieved re-attendance of 72.2% and telephone interview with a further 22.4%. Information on the remaining individuals were collected through family members and only 0.4% of individual were lost to follow-up. Informed, written consent was obtained prior to commencement of study measurement. Volunteers were interviewed by a trained nurse to collect data on demographic, socioeconomic, health behaviours and medical conditions. The blood samples were collected from the participants in fasting state. Breakfast was provided for the participants after taking blood samples and after being guided to stations designed for the interview and physical measurements including, anthropometry, blood pressure, 12-lead electrocardiography, pulmonary function testing, and chest radiography. A vacutainer tube was used to draw blood samples. C-reactive protein, glucose, lipids, markers of liver were determined automatically in the hospital laboratory using standard clinical laboratory methods.

Ethical approval was obtained from Guangzhou Medical Association Ethics Committee. In total, across three phases of the study, 30,499 participants were

recruited. Since more precise sleep questions were included in phase 3 of the study, data from phase three, which involved 10,088 participants, were used for this study.

2.4.2 Variables

Data on sleep duration were acquired via self-administered questionnaire. The question formulation was "During the past 24-hour, how many hours of sleep did you get at night?" The participants were classified in five sleep categories; <6 hours, 6-<7 hours, 7-<8 hours, 8-<9 hours, and ≥9 hours. Sleep data from only phase three of the GBCS were used as previous sleep data collected in earlier phases included total sleep duration that included naps. In phase three only, data were collected regarding night-time sleep and was more reflective of published studies.

The aim of the current study was to assess the factors associated with short and long sleep duration. The list of these factors was chosen based on the data available of a particular variable in the study and also based on literature search and findings of the studies that assessed similar trends. All other independent variables were categorised into two groups and the reference category is specified. Waist circumference was measured in horizontal state, and the measure of smallest circumference between ribs and iliac crest was recorded. Obesity was determined by waist circumference according to the International Diabetes Federation (IDF) guidance on waist circumference thresholds as a measure of central adiposity for Chinese (≥80 cm for women, ≥90 cm for men).[232] Shimadzu CL-8000 Automatic Chemical Analyser was used to determine glucose level in the hospital laboratory. Type 2 diabetes was defined as fasting blood glucose ≥7.0 mmol/l or being on glucose-lowering medications.[233]

Blood pressure was measured three times with Omron 705CP sphygmomanometer in the seated state, giving 1 to 3 minutes break between each reading. The average of the three readings was used for analysis. Hypertension was defined as systolic blood pressure (SBP) ≥140 mmHg or diastolic blood pressure (DBP) ≥90 mmHg or being on blood pressure lowering medications.[234] The Chinese validated International Physical Activity Questionnaire (IPAQ short version) was utilised to assess the level of physical activity, which was subsequently dichotomised into "active" and "non-active".[235]

2.4.3 Statistical Analysis

The first aim of the current study was to assess the factors (i.e. socio-demographic, socio-economic, health behaviour, medical conditions) associated with short and long sleep duration. A list of the factors (age, gender, marital status, education level, income level, smoking, alcohol consumption, physical activity, obesity, hypertension, and diabetes) was chosen based on the data available of a particular variable in the study and also based on a literature search and findings of the studies that assessed similar trends (Kruger and Friedman,[63] Magee and colleagues,[210] Ryu and colleagues[230]).

After deciding upon inclusion of appropriate factors, two steps were taken to assess the association of such factors with sleep duration. The first step involved, looking at the crude association between predictor variables (age (≥65 years, <65 years (ref)), gender (female, male (ref)), marital status (widowed, married (ref)), education level (<secondary school, ≥secondary school (ref)), income level (<15,000 Yuan, ≥15,000 Yuan (ref)), smoking status (ever smoking, never smoking (ref)), alcohol consumption (ever drinking, never drinking (ref)), physical activity (active, not active (ref)), obesity (yes, no (ref)), hypertension (yes, no (ref)), diabetes (yes, no (ref)), and categories of

sleep duration (<6 hours, 6-<7 hours, 8-<9 hours, ≥9 hours), taking category of 7-8 hours as a reference (evidence shows that sleeping between 7 to 8 hours was associated with the lowest mortality;[3] therefore, this was used as the reference group), using multinomial logistic regression. All the predictor variables were categorised into two groups and the reference category is specified. The reference category was selected based on the research question. The second step, entering all the above variable into one single model, in order to determine the independent association between factor(s) with short sleep duration, or long sleep duration, or both.

The other objective of the study was to assess the association between sleep duration (exposure) and obesity (outcome), hypertension (outcome), and diabetes (outcome). The above associations were adjusted for a number of potential confounders. The selection of confounding variables was based on the results from other previous studies[33, 140] that evaluated similar associations and also was based on comparing adjusted and unadjusted effect estimates (e.g. 10% change in OR).[236] If the relative change after adjustment for a certain variable was greater than 10 percent, then the variable was selected. After exclusion of variables that were found not to be confounders, the association between sleep duration, obesity, hypertension and diabetes were adjusted for following variables; age, gender, marital status, education level, income level, smoking, alcohol consumption, physical activity, obesity (not appropriate for assessing the association between sleep duration and obesity), hypertension (not appropriate for assessing the association between sleep duration and hypertension), and diabetes (not appropriate for assessing the association between sleep duration and diabetes).

The chi-square test was used to assess the association between characteristics of the participants (i.e. age, gender, marital status, education, annual income, physical activity, smoking status, alcohol use, obesity, hypertension, diabetes) by sleep duration (i.e. <6 hours, 6-<7 hours, 7-<8 hours, 8-<9 hours, ≥9 hours). The design of the present study is cross-sectional. The data were analysed using SPSS version 18 (SPSS, Chicago, IL) and results are reported as odds ratios (with 95% confidence intervals). A 2-tailed p value of less than 0.05 was considered statistically significant.

The analysis of data on this chapter was conducted in three steps. 1) The univariable analyses between independent variables (age, gender, marital status, education level, income level, smoking, alcohol consumption, physical activity, obesity, hypertension, and diabetes) and dependant variables (sleep duration categories of <6 hours, 6-<7 hours, 8-<9 hours, ≥9 hours compared with 7-8 hours) were assessed. 2) The multivariable analyses with all the independent variables from above and sleep categories as dependant variables were assessed. 3) The multivariable analyses between sleep duration categories as independent variables and medical conditions including obesity, hypertension, and diabetes as dependant variables, adjusted for age, gender, marital status, education level, income level, smoking, alcohol consumption, physical activity, obesity, hypertension, and diabetes were assessed.

2.4.3.1 Univariable analyses

The univariate association between several independent variables including, age, gender, marital status, education level, income level, smoking status, alcohol consumption, physical activity, obesity, hypertension and diabetes with sleep duration was assessed. Multinomial logistic regression was used to calculate odds ratios to

assess the association between independent variables and with short or long sleep duration compared to 7-<8 hours of sleep per night (reference group).

When disease incidence is rare (<10%), odds ratios can be used to estimate relative risk. In settings such as cross-sectional studies, where the population denominator is unknown and there are also uncertainties about the population from which subjects are drawn, the cases and exposure cannot be certain due to lack of knowledge about the actual population. Logistic regression, which utilises the logs of the odds ratio can be used to calculate odds ratios, while controlling for several potential confounders. However, using logistic regression to compute an estimated odds ratio and the subsequent interpretation of this estimate as a relative risk can be problematic when the outcome is more common. In studies of common outcomes, the estimated odds ratio can substantially overestimates the relative risk. This can mean there are issues in the interpretation of either the associated risk (believing the exposure is of greater harm than is the case) or risk reduction (believing the exposure is of great benefit than is the case) depending on the analyses being performed.

2.4.3.2 Multivariable analyses

All the independent variables listed above was entered into one single model, in order to determine the independent association between factor(s) with short sleep duration, or long sleep duration, or both. The multinomial logistic regression was used to calculate the odds ratios.

2.4.3.3 Multivariable analyses between sleep duration, obesity, hypertension and diabetes

The association between sleep duration as an independent variable with obesity, hypertension, and diabetes as an outcome variable were assessed after adjusting for multiple potential confounders (age, gender, marital status, education level, income level, smoking, alcohol consumption, physical activity). The association between hypertension, obesity, and diabetes with sleep duration was then assessed after stratifying by age and gender based on published literature demonstrating age and gender differences.

2.5 Results

The descriptive characteristics of the participants within each sleep-duration category are presented in Table 2-1. Interestingly, only 30% of older adults reported sleeping between 7 to 8 hours per night ('normal' sleepers), while 14% were short sleepers (<6 hours of sleep per night), and 10% were long sleepers (≥9 hours of sleep per night). Compared to sleep category of 7 to 8 hours of sleep, 38.8% of adults aged 65 years and older (vs. 23.9%), 81% of females (vs. 74.9%), 23.8% widowed (vs. 15.4%), 76.1% of those with lower education (vs. 61.5%), 81.3% of those with lower annual income (vs. 73.6%), 12.0% diabetics (vs. 9.9%), were short sleepers while 23.2% of ever smokers were long sleepers (vs. 17.7%). Physical activity levels, obesity, and diabetes did not significantly differ across different sleep categories.

Table 2-1. Descriptive characteristics of 10,088 Chinese adults aged ≥50 years according to total sleep duration, Guangzhou Biobank Cohort Study, 2003-2008. Characteristics of participants by sleep duration using chi square test.

	Total sleep duration						
Characteristics	**<6 hrs**	**6-<7 hrs**	**7-<8 hrs**	**8-<9 hrs**	**≥9 hrs**	**Total**	***p* value**
	(n =1,467) 14.5%	(n = 2,256) 22.4%	(n = 2,955) 29.3%	(n = 2,337) 23.2%	(n = 992) 9.8%	N =10,088	
Age (%)							<0.001
<65yrs	61.2	70.1	76.5	75.4	70.1	71.9	
≥65yrs	38.8	29.9	23.5	24.6	29.9	28.1	
Sex (%)							<0.001
Male	19.0	23.7	25.1	28.0	34.0	25.4	
Female	81.0	76.3	74.9	72.0	66.0	74.6	
Marital status (%)							<0.001
Married	76.2	81.6	84.6	85.4	83.8	82.8	
Widowed	23.8	18.4	15.4	14.6	16.2	17.2	
Education							<0.001
< Secondary School	76.1	67.7	61.5	61.6	66.0	65.5	
≥ Secondary School	23.9	32.3	38.5	38.4	34.0	34.5	
Annual Income (%)							<0.001
<15,000 Yuan	81.3	78.7	73.6	72.7	75.3	28.0	
≥15,000 Yuan	18.7	21.3	26.4	27.3	24.7	72.0	
Physical activity (%)							0.087
Not active	37.6	35.2	35.0	33.8	37.3	7.9	
Active	62.4	64.8	65.0	66.2	62.7	92.1	
Smoking status (%)							<0.001
Never	85.5	82.7	82.3	81.1	76.8	82.0	
Ever	14.5	17.3	17.7	18.9	23.2	18.0	
Alcohol use (%)							0.004
Never	53.2	49.8	47.3	48.8	51.1	49.4	
Ever	46.8	50.2	52.7	51.2	48.9	50.6	
Obesity (%)							0.281
Yes	33.8	31.9	31.1	31.0	33.4	31.9	
No	66.2	68.1	68.9	69.0	66.6	68.1	
Hypertension (%)							<0.001
Yes	42.3	40.6	36.1	39.4	42.3	39.1	
No	57.7	59.4	63.9	60.6	57.7	60.9	
Diabetes (%)							0.053
Yes	12.0	11.2	9.9	9.3	10.7	10.5	
No	88.0	88.8	90.1	90.7	89.3	89.5	

Table 2-2. Odds ratios and 95% confidence intervals from the univariate multinomial logistic regression models predicting sleep duration.

	Self-reported Sleep Hours			
	<6 hrs vs. 7-8 hrs	**6-<7 hrs vs. 7-8 hrs**	**8-<9 hrs vs. 7-8 hrs**	**≥9 hrs vs. 7-8 hrs**
	Risk ratio (95% confidence interval)	**Risk ratio (95% confidence interval)**	**Risk ratio (95% confidence interval)**	**Risk ratio (95% confidence interval)**
Age (years)				
≥ 65 years	2.06 (1.80 – 2.35)**	1.38 (1.22 – 1.56)**	1.06 (0.93 – 1.20)	1.39 (1.18 – 1.63)**
< 65 years (ref)	1.00	1.00	1.00	1.00
Sex				
Female	1.43 (1.22 – 1.67)**	1.07 (0.94 – 1.24)	0.86 (0.76 – 0.97)*	0.65 (0.55 – 0.76)**
Male (ref)	1.00	1.00	1.00	1.00
Marital status				
Widowed	1.71 (1.46 – 2.00)**	1.24 (1.07 – 1.43)	0.93 (0.80 – 1.09)	1.06 (0.87 – 1.29)
Married (ref)	1.00	1.00	1.00	1.00
Education level				
< Secondary School	1.98 (1.72 – 2.29)**	1.31 (1.16 – 1.47)**	1.00 (0.89 – 1.12)	1.21 (1.04 – 1.41)*
≥ Secondary School (ref)	1.00	1.00	1.00	1.00
Income level				
< 15,000 Yuan	1.56 (1.33 – 1.83)**	1.32 (1.15 – 1.51)**	0.95 (0.84 – 1.08)	1.09 (0.92 – 1.29)
≥ 15,000 Yuan	1.00	1.00	1.00	1.00
Smoking status				
Ever smoking	1.27 (1.07 – 1.51)**	1.02 (0.89 – 1.18)	0.92 (0.80 – 1.06)	0.71 (0.59 – 0.85)**
Never smoking (ref)	1.00	1.00	1.00	1.00
Alcohol consumption				
Ever drinking	1.26 (1.11 – 1.43)**	1.10 (0.99 – 1.23)	1.06 (0.95 – 1.18)	1.16 (1.00 – 1.34)*
Never drinking (ref)	1.00	1.00	1.00	1.00
Physical activity				
Active	1.12 (0.98 – 1.27)	1.01 (0.90 – 1.13)	0.95 (0.84 – 1.06)	1.10 (0.95 – 1.28)
Not active (ref)	1.00	1.00	1.00	1.00
Obesity	1.14 (0.90 – 1.42)	1.10 (0.90 – 1.34)	0.94 (0.77 – 1.16)	1.23 (0.96 – 1.59)
Hypertension	1.29 (1.14 – 1.47)**	1.20 (1.07 – 1.35)**	1.15 (1.02 – 1.28)*	1.29 (1.12 – 1.50)**
Diabetes	1.23 (1.01 – 1.51)*	1.15 (0.96 – 1.37)	0.93 (0.77 -1.12)	1.09 (0.86 – 1.38)

* $p < 0.05$, ** $p < 0.01$

Table 2-3. Odds ratios and 95% confidence intervals from the fully adjusted multinomial logistic regression model predicting sleep duration.

	Self-reported Sleep Hours			
	<6 hrs vs. 7-8 hrs	**6-<7 hrs vs. 7-8 hrs**	**8-<9 hrs vs. 7-8 hrs**	**≥9 hrs vs. 7-8 hrs**
	Risk ratio (95% confidence interval)	**Risk ratio (95% confidence interval)**	**Risk ratio (95% confidence interval)**	**Risk ratio (95% confidence interval)**
Age (years)				
≥ 65 years	1.87 (1.59 – 2.18)**	1.32 (1.15 – 1.53)**	1.02 (0.88 – 1.18)	1.13 (0.94 – 1.36)
< 65 years (ref)	1.00	1.00	1.00	1.00
Sex				
Female	1.37 (1.09 – 1.73)**	1.06 (0.87 – 1.29)	0.83 (0.69 – 1.00)	0.58 (0.46 – 0.74)**
Male (ref)	1.00	1.00	1.00	1.00
Marital status				
Widowed	1.22 (1.02 – 1.45)*	1.00 (0.85 – 1.18)	0.91 (0.77 – 1.08)	1.06 (0.86 – 1.32)
Married (ref)	1.00	1.00	1.00	1.00
Education level				
< Secondary School	1.65 (1.41 – 1.93)**	1.21 (1.06 – 1.37)**	1.01 (0.89 – 1.14)	1.14 (0.97 – 1.35)
≥ Secondary School (ref)	1.00	1.00	1.00	1.00
Income level				
< 15,000 Yuan	1.16 (0.97 – 1.38)	1.20 (1.04 – 1.39)*	0.97 (0.85 – 1.11)	1.14 (0.97 – 1.35)
≥ 15,000 Yuan (ref)	1.00	1.00	1.00	1.00
Smoking status				
Ever smoking	0.89 (0.69 – 1.14)	0.99 (0.80 – 1.22)	0.96 (0.78 – 1.18)	0.97 (0.75 – 1.25)
Never smoking (ref)	1.00	1.00	1.00	1.00
Alcohol consumption				
Ever drinking	0.92 (0.80 – 1.06)	0.94 (0.83 – 1.06)	0.92 (0.81 – 1.03)	0.82 (0.70 – 0.97)*
Never drinking (ref)	1.00	1.00	1.00	1.00
Physical activity				
Active	1.13 (0.98 – 1.30)	0.99 (0.87 – 1.20)	0.93 (0.82 – 1.05)	0.97 (0.83 – 1.14)
Not active (ref)	1.00	1.00	1.00	1.00
Obesity	0.91 (0.72 – 1.16)	0.97 (0.78 – 1.21)	0.94 (0.75 – 1.17)	1.30 (0.99 – 1.71)
Hypertension	1.08 (0.94 – 1.24)	1.14 (1.00 – 1.28)*	1.15 (1.01 – 1.29)*	1.14 (0.97 – 1.34)
Diabetes	1.10 (0.89 – 1.37)	1.07 (0.88 – 1.29)	0.88 (0.72 -1.07)	1.00 (0.78 – 1.28)

* $p < 0.05$, ** $p < 0.01$ Note: All the independent variables were all fitted into one single model.

Table 2-4. Odds ratios (95% confidence intervals) for obesity, hypertension, and diabetes by reported usual sleep duration in the whole sample.

	Obesity Risk ratio (95% confidence interval)[a]	Hypertension Risk ratio (95% confidence interval)[b]	Diabetes Risk ratio (95% confidence interval)[c]
< 6 hours	0.92 (0.79 – 1.06)	1.09 (0.95 – 1.26)	1.11 (0.90 – 1.37)
6-<7 hours	0.94 (0.83 – 1.07)	1.15 (1.01 – 1.30)*	1.08 (0.89 – 1.30)
7-<8 hours (ref)	1.00	1.00	1.00
8-<9 hours	1.02 (0.89 – 1.15)	1.14 (1.01 – 1.29)*	0.88 (0.72 – 1.07)
≥9 hours	1.19 (1.00 – 1.40)*	1.13 (0.96 – 1.33)	1.00 (0.78 – 1.29)

[a] Adjusted for age, gender, marital status, education level, income level, smoking, alcohol consumption, physical activity, hypertension, and diabetes. [b] Adjusted for age, gender, marital status, education level, income level, smoking, alcohol consumption, physical activity, obesity, and diabetes, [c] Adjusted for age, gender, marital status, education level, income level, smoking, alcohol consumption, physical activity, obesity, and hypertension. *p<0.05

Table 2-5. Odds ratios (95% confidence intervals) for hypertension, obesity, and diabetes by reported usual sleep duration in males by age (<65/≥ 65 years).

	Obesity Risk ratio (95% confidence interval)[a]	Hypertension Risk ratio (95% confidence interval)[b]	Diabetes Risk ratio (95% confidence interval)[c]
< 65 years			
< 6 hours (n = 100**)**	0.96 (0.52 – 1.76)	1.25 (0.79 – 1.98)	1.14 (0.55 – 2.34)
6-<7 hours (n = 279**)**	1.12 (0.74 – 1.68)	1.13 (0.82 – 1.56)	1.11 (0.67 – 1.83)
7-<8 hours (n = 424**, ref)**	1.00	1.00	1.00
8-<9 hours (n = 369**)**	0.79 (0.53 – 1.18)	1.22 (0.91 – 1.64)	1.02 (0.64 – 1.65)
≥9 hours (n = 171**)**	0.95 (0.58 – 1.57)	1.10 (0.75 – 1.61)	1.00 (0.54 – 1.84)
≥ 65 years			
< 6 hours (n = 151**)**	0.83 (0.50 – 1.37)	1.10 (0.72 – 1.67)	1.09 (0.62 – 1.92)
6-<7 hours (n = 205**)**	0.61 (0.38 – 0.99)*	1.55 (1.05 – 2.29)*	0.75 (0.42 – 1.31)
7-<8 hours (n = 248**, ref)**	1.00	1.00	1.00
8-<9 hours (n = 229**)**	0.69 (0.44 – 1.10)	0.99 (0.68 – 1.43)	0.61 (0.35 – 1.08)
≥9 hours (n = 131**)**	0.50 (0.28 – 0.91)*	1.22 (0.79 – 1.90)	0.79 (0.42 – 1.51)

[a] Adjusted for marital status, education level, income level, smoking, alcohol consumption, physical activity, hypertension, and diabetes. [b] Adjusted for marital status, education level, income level, smoking, alcohol consumption, physical activity, obesity, and diabetes. [c] Adjusted for marital status, education level, income level, smoking, alcohol consumption, physical activity, obesity, and hypertension. *p<0.05

Table 2-6. Odds ratios (95% confidence intervals) for hypertension, obesity, and diabetes by reported usual sleep duration in females by age (<65/≥ 65 years).

	Obesity Risk ratio (95% confidence interval)[a]	Hypertension Risk ratio (95% confidence interval)[b]	Diabetes Risk ratio (95% confidence interval)[c]
< 65 years			
< 6 hours (n = 779**)**	0.87 (0.72 – 1.06)	1.14 (0.94 – 1.39)	1.25 (0.92 – 1.70)
6-<7 hours (n = 1,259**)**	0.97 (0.82 – 1.15)	1.07 (0.90 – 1.27)	0.93 (0.70 – 1.23)
7-<8 hours (n = 1,782**, ref)**	1.00	1.00	1.00
8-<9 hours (n = 1,347**)**	1.06 (0.91 – 1.25)	1.19 (1.01 – 1.41)*	0.82 (0.62 – 1.09)
≥9 hours (n = 502**)**	1.45 (1.16 – 1.80)**	1.24 (0.99 – 1.56)	1.12 (0.78 – 1.60)
≥ 65 years			
< 6 hours (n = 409**)**	1.00 (0.75 – 1.33)	0.94 (0.70 – 1.26)	0.98 (0.65 – 1.47)
6-<7 hours (n = 459**)**	0.94 (0.71 – 1.24)	1.16 (0.87 – 1.54)	1.55 (1.07 – 2.24)*
7-<8 hours (n = 431**, ref)**	1.00	1.00	1.00
8-<9 hours (n = 331**)**	1.17 (0.86 – 1.58)	1.01 (0.74 – 1.38)	1.07 (0.70 – 1.63)
≥9 hours (n = 151**)**	1.13 (0.76 – 1.67)	0.88 (0.59 – 1.32)	0.88 (0.50 – 1.58)

[a] Adjusted for marital status, education level, income level, smoking, alcohol consumption, physical activity, hypertension, and diabetes. [b] Adjusted for marital status, education level, income level, smoking, alcohol consumption, physical activity, obesity, and diabetes. [c] Adjusted for marital status, education level, income level, smoking, alcohol consumption, physical activity, obesity, and hypertension. *p<0.05, **p<0.01

2.5.1 Univariable analyses

Odds ratios and 95% confidence intervals from the univariate analysis are presented in Table 2-2. The results indicate that individuals aged 65 years and older were more likely to sleep <6 hours (OR 2.06, 95% CI 1.80 – 2.35), 6-<7 hours (OR 1.38, 95% CI 1.22 – 1.67), and ≥9 hours (OR 1.39, 95% CI 1.18 – 1.63) compared to individuals aged below 65 years (prevalence percentages: <6 hours; 38.8% ≥65 years vs. 61.2% <65 years, ≥9 hours; 29.9% ≥65 years vs. 70.1% <65 years). Females had a higher risk of shorter sleep duration (<6 hours, OR 1.43, 95% CI 1.22 – 1.67), compared to males (prevalence percentages: 81% females vs. 19% males). Compared to married individuals, those widowed had a higher risk of being short sleepers (OR 1.71, 95% CI 1.46 – 2.00) (prevalence percentages: 23.8% widowed vs. 76.2% married). Having an education level of lower than secondary school was associated with sleep duration of <6 hours (OR 1.98, 95% CI 1.72 – 2.29), 6-<7 hours (OR 1.31, 95% CI 1.16 – 1.47), and ≥9 hours (OR 1.21, 95% CI 1.04 – 1.41), compared to higher education level (≥secondary school) (prevalence percentages: <6 hours; 76.1% lower education vs. 23.9% higher education, 6-<7 hours; 67.7% lower education vs. 32.3% higher education, ≥9 hours; 66.0% lower education vs. 34.0% higher education). Compared to higher annual income level (≥15,000 Yuan), lower annual income level (<15,000 Yuan) was also associated with sleep duration of <6 hours and 6-<7 hours (prevalence percentages: <6 hours; 81.3% lower income vs. 18.7% higher income, 6-<7 hours; 78.7% lower income vs. 21.3% higher income). Ever smokers had increased risk for short (<6 hours) sleep duration (OR 1.27, 95% CI 1.07 – 1.51), compared to never smokers (prevalence percentages: 14.5% ever smokers vs. 85.5% never smokers). Those who ever consumed alcohol had a higher risk of being both short sleepers (<6

hours) and long (≥9 hours) sleepers, compared to those who never consumed alcohol, (prevalence percentages: <6 hours; 46.8% ever drinkers vs. 53.2% never drinkers, ≥9 hours; 50.6% ever drinkers vs. 49.4% never drinkers). Hypertension was also associated with all 5 sleep categories (prevalence percentages: <6 hours, 42.3% hypertension vs. 57.7% no hypertension, 6-<7 hours; 40.6% hypertension vs. 59.4% no hypertension, 8-<9 hours; 39.4% hypertension vs. 60.6% no hypertension, ≥9 hours; 43.3% hypertension vs. 57.7% no hypertension). However, individuals with diabetes were more likely to be short sleepers (<6 hours), (OR 1.23, 95% CI 1.01 – 1.51), compared to individuals without diabetes (prevalence percentages: 12.0% diabetes vs. 88.0% no diabetes). No significant association was found between physical activity, obesity and sleep.

2.5.2 Multivariable analyses

The multivariate adjustment between socio-demographic, socio-economic, lifestyle and medical conditions variables was also assessed. Some associations that were found to be significant in univariate model no longer remained significant. A summary of results is presented in Table 2-3. Individuals who were aged 65 years and older were more likely to sleep <6 hours (OR 1.87, 95% CI 1.59 – 2.18) and sleep 6-<7 hours (OR 1.32, 95% CI 1.15 – 1.53), compared to individuals aged below 65 years. Females had a higher risk for <6 hours sleep (OR 1.37, 95% CI 1.09 – 1.73), compared to males. Those widowed had higher risk of sleep duration of <6 hours (OR 1.22, 95% CI 1.02 – 1.45), compared to married individuals. Individuals with lower education level (<secondary school) were more likely to sleep <6 hours (OR 1.65, 95% CI 1.41 – 1.93) and 6-<7 hours (OR 1.21, 95% CI 1.06 – 1.37), compared to individuals with higher education level (≥ secondary school). Compared to higher income (≥15,000 Yuan)

level, lower annual income (<15,000 Yuan) was associated with sleep duration of 6-<7 hours (OR 1.20, 95% CI 1.04 – 1.39). Those who ever consumed alcohol had a lower risk for sleep duration of ≤9 hours, (OR 0.82, 95% CI 0.70 – 0.97), compared to those who never consumed alcohol. Individuals with hypertension were more likely to sleep 6-<7 hours (OR 1.14, 95% CI 1.00 – 1.28) and sleep 8-<9 (OR 1.15, 95% CI 1.01 – 1.29), compared to individuals without hypertension.

2.5.3 Multivariabe analyses between sleep duration, obesity, hypertension and diabetes

Results from multivariate analysis demonstrated that compared to normal sleep duration (7-8 hours), long sleep duration (≥9 hours) was significantly associated with obesity after adjustment for potential confounders (OR 1.19, 95% CI 1.00 – 1.40). Moreover, sleep duration of 6-<7 hours (OR 1.15, 95% CI 1.01 – 1.30) and 8-<9 hours (OR 1.14, 95% 1.01 – 1.29), compared to normal sleep duration (7-8 hours), were associated with increased risk of hypertension (Table 2-4). No association was detected between sleep duration and diabetes in whole sample. The analysis was re-ran by stratifying for age and gender and results demonstrated that in males aged 65 years and older, short (6-<7 hours) (OR 0.61, 95% CI 0.38 – 0.99) and long sleep duration (≥9 hours) (OR 0.51, 95% CI 0.28 – 0.91), compared to normal sleep duration (7-8 hours) were inversely associated with obesity (Table 2-5). In younger (<65 years) females, hypertension was associated with sleep duration of 8-<9 hours (OR 1.45, 95% CI 1.16 – 1.80) and sleep duration of ≥9 hours (OR 1.30, 95% CI 1.04 – 1.63), compared to normal sleep duration (7-8 hours) (Table 2-6). Moreover, compared to normal sleep duration (7-8 hours), sleep duration of ≥9 hours was strongly associated with obesity among these women (OR 1.45, 95% CI 1.16 – 1.80). Thus, long sleep has an important factor associated with obesity and hypertension in younger women in the

GBCS. On the other hand, in females aged 65 years and older, a sleep duration of 6-<7 hours was associated with an increased risk of diabetes (OR 1.55, 95% CI 1.07 – 2.24), compared to sleep duration of 7-8 hours (Table 2-6). The findings suggest an important contribution of age and gender to the associations between sleep and important chronic disorders.

2.6 Discussion

Evidence indicates that both sleep quantity and quality play an important role in health and well-being. Results from previous studies indicate that on average the mean sleep duration of older (≥50 years) individuals from China[237] (mean usual sleep duration = 5.5 hours per night) is lower compared to Spain[238] (mean usual sleep duration = 8.1 hours per night), US[239] (mean usual sleep duration = 6.8 hours per night), and Australia[240] (mean usual sleep duration = 8.3 per night). It can be suggested that demographic, socio-economic, and medical conditions may have an influence on sleep duration across different countries.

The findings of the present study showed that 37% of older Chinese people reported sleeping 6 hours or less per night. It was also found that being female, older, being widowed, having a lower education, and a lower income level are strongly associated with short sleep duration, while hypertension is strongly associated with long sleep duration. Additionally, the results of the logistic regression model controlling for age, gender, marital status, education level, income level, smoking, alcohol consumption, physical activity, obesity, hypertension and diabetes showed that long sleep duration was significantly associated with obesity and both short and long sleep duration were associated with hypertension in the whole sample. No significant association was found between sleep duration and diabetes in the whole sample. The results of my stratified analysis by gender and age showed that there was an inverse association between short and long sleep duration and obesity among males aged 65 years and older. In females, aged below 65 years, only long sleep duration was positively associated with obesity. Short sleep duration was associated with hypertension among older males, while in younger females, long sleep duration was associated with

increased risk of hypertension. Moreover, in older females, only short sleep duration was positively associated with increased risk of diabetes.

2.6.1 Demographic and socio-economic factors and sleep

2.6.1.1 Age

In the present study, individuals who were aged 65 years and older were 87% (95% CI 1.59 – 2.18) more likely sleep <6 hours and also 32% more likely to sleep 6-<7 hours (95% CI 1.15 – 1.53), compared to those aged <65 years. Several studies have noted a relationship between ageing and shorter sleep duration. Explanations for this observation have been discussed above (see *Chapter 1*). Additionally, sleep problems, and especially insomnia are common in older individuals.[22] The results from analyses of cross-sectional data from the Established Populations for Epidemiologic Studies of the Elderly (EPESE), involving 9,000 American participants, demonstrated that almost half the individuals aged 65 years or older had longer sleep latency and difficulties in sleep continuity.[241] Results from another study from US, among 10,050 participants with mean age of 74.4 years, suggested that sleep problems including; difficulties falling sleep (36.7%) difficulties maintaining asleep (28.7%), and early morning awaking (19.1%) are relatively pevalent.[242] However, following multivariate adjustment for chronic conditions, the prevalence of sleep problems reduced significantly. This suggests that the increased numbers of co-morbid conditions among older individuals might be responsible for poor sleep quality rather than ageing per se.[243] Apart from chronic conditions, ageing is also associated with circadian rhythm changes, which could be responsible for low sleep efficiency, poor sleep quality, and short sleep duration among older adults.[21] Other endogenous factors such as retirement may also change the patterns of waking and sleeping time among older individuals.

My analysis shows that shorter sleep duration with ageing in the GBCS cohort was independent of a number of factors including common chronic disorders such as obesity, hypertension and diabetes. This suggests that ageing per se is associated with shorter sleep duration supporting a biological explanation. However, there is a need for future studies to examine sleep duration and quality in more detail including an assessment of common sleep disorders such as insomnia and obstructive sleep apnoea.

2.6.1.2 Gender

The results from both univariate and multivariate analysis showed that, compared to male gender, female gender was associated with 37% (95% CI 1.09 – 1.73) increased risk for short sleep (<6 hours). It was previously found that women may be more susceptible to develop sleep problem compared to men.[244] Results of a recently published meta-analysis on the impact of gender differences in insomnia, including 31 studies representing 1,265,015 participants showed that compared to male gender, being female is associated with an increased risk for insomnia (OR 1.41, 95% CI 1.28 - 1.55).[245] The exact mechanism underlying the effect of gender on sleep disturbance is unknown. It is believed that difficulties initiating sleep or maintaining sleep may be a manifestation of psychiatric disorders such as anxiety and depression and women are more vulnerable to mental health problems;[244] therefore it was previously suggested that anxiety and depression symptoms may be causal factors for development of sleep disturbance such as insomnia among women.[244] However, the prior hypothesis cannot be fully accepted since the association between female gender and insomnia still remained significant even after controlling for psychiatric status.[246] Depressed women are more likely to report somatic symptoms such as body pain and sleep disturbances compared to men.[247] Sex differences in sleep symptoms could be due to the specific role of women as caregivers that may predispose them for higher risk of emotional

distress.[245] Additionally, women have an increased vulnerability for sleep disturbances due to the menopause.[248-250] It has been previously found that menopause is associated with changes in sleep architecture, which may increase sleep complaints among women. In a study of 436 healthy women, Hollander and colleagues found that hot flushes and oestradiol levels were strong predictors for poor sleep (OR 1.52, 95% CI 1.08 - 2.12).[249] The negative impact of the menopause on sleep duration and sleep efficiency may increase the risk for weight gain and cause further sleep impairment.[248]

2.6.1.3 Marital status

The current study found, in the univariate analysis, that compared to married individuals, those who were widowed had 71% (95% CI 1.46 – 2.00) increased risk for short sleep duration (<6 hours). In the multivariate analysis, this attenuated to 22% (95% CI 1.02 – 1.45). Similar to findings from this study, previous evidence also indicates that being single or divorced/widowed was associated with increased risk for short sleep duration among 49,405 Australian adults aged 45 to 65 years (OR 1.47, 95% CI 1.31 - 1.66).[210] Ursin and colleagues studied 8,860 subjects, aged 40 to 45 years, and reported that married men were more likely to sleep longer than single men.[239] The analysis of data collected over 34 years from habitants of Alameda Country in California demonstrated that non-married status had a 2-fold higher risk of short sleep duration (≤6 hours).[251] Kronholm and colleagues[252] assessed the determinants of both short and long sleep duration in 8,028 Finnish adults and reported that the prevalence of short sleep (≤6 hours) duration was higher among non-married/divorced group (13% among short sleepers vs. 6.4% and 10.0% among normal and long sleepers).[252] In contrast, Patel and colleagues[153] previously investigated the factors that correlate with long sleep duration in 60,028 middle-aged women, and they reported that compared to married women, those who have been divorced or never

have been married had higher risk of being long sleepers (divorced; OR 1.21, 95% CI 1.10 – 1.32 and never married; OR 1.37, 95% CI 1.22 – 1.54). It is difficult to explain the reverse findings by Patel and colleague, it can be argued that never married or divorced women are less likely to have a role as caregiver and in particular never married women may not have any children, as it was previously found that increased number of children may reduce total sleep duration.[210]

2.6.1.4 Education and income level

The present study showed that compared to those with higher education level, individuals with a lower education level (<secondary school) were 65% (95% CI 1.41 – 1.93) more likely to belong to sleep category of <6 hours and also 21% (95% CI 1.07 – 1.37) more likely to sleep 6-<7 hours. Lower annual income (<15,000 Yuan) was associated with 20% (95% CI 1.04 – 1.39) higher risk for sleep duration of 6-<7 hours. In line with my findings, Friedman and colleagues[253] studied 94 women, aged 61 to 90 years and found that more years of education and a higher household income was significantly associated with a decrease in sleep latency (years of education; $\beta = -0.50$, $p<0.001$, household income; $\beta = -0.33$, $p<0.05$) and an increase in sleep efficiency (years of education; $\beta = 0.21$, $p<0.05$, household income; $\beta = 0.26$, $p<0.05$). This association remained significant even after controlling for potential confounders including: demographic factors, health status, and psychosocial characteristics. In a similar study, Lauderdale and colleagues[126] objectively (using actigraphy) assessed sleep patterns of 669 participants from the Coronary Artery Risk Development in Young Adults (CARDIA) study. Participants were aged 38 to 50 years, and 58% were women. The authors found that income was significantly associated with sleep latency (β 3.13, 95% CI 4.87 - 1.39, $p<0.001$) and sleep efficiency (β 0.79, 95% CI 0.18 - 1.41, $p<0.01$) among these individuals.

The effect of socio-economic status on sleep can potentially be explained by the potential impact of psychiatric disorders and in particular, depression.[254] Lower education and income levels are associated with an increased risk for anxiety and depression symptoms that may have an inverse effect on both sleep quantity and quality.[253] Surprisingly, the psychological impairment as a result of lower education level was found to be more severe compared to the psychological impairment as a result of lower income level.[253] It can therefore be argued that education levels are likely to have a stronger impact on sleep. Educated individuals are more likely to seek medical treatment for their sleep problems. Acquiring higher education needs many years of effort and its impact on health and well-being is potentially lasting, whereas the association between health and income level may be on-going. In order to achieve a higher salary, individuals with lower income level may tend to be hired in jobs that require shiftwork, which may result inconsistent sleep habits However, such hypotheses may not be applicable to the individuals in present study, since they were at retirement and were no longer working. The pathways linking education and income with sleep require further evaluation. A qualitative approach is necessary to explore potential linking factors across different age groups.

2.6.2 Lifestyle behaviours and sleep

2.6.2.1 Alcohol consumption

In univariate analyses, I found that alcohol consumption was positively associated with both short and long sleep duration. However, in the full model, compared to never alcohol consumption, ever alcohol consumption was associated with lower risk (OR 0.82, 95% CI 0.70 – 0.97) for sleep duration of ≤9 hours. Evidence suggests that there is a link between sleep duration and alcohol consumption.[255] Recently, Chaput and

colleagues[255] investigated the relation between sleep duration and alcohol consumption in a representative sample of 703 men and women aged between 18 to 64 years. Alcohol consumption was assessed using a 3-day food record. According to relevant guidelines, alcohol intake was dichotomised on the basis of whether it exceeded the recommended limit for men and women. Sleep duration was assessed using a self-administered questionnaire. The results revealed that sleeping 6 hours and less per night was associated with excessive alcohol consumption among men and women (OR 1.87, 95% CI 1.03 – 3.54) and the prevalence of binge drinking was higher among short sleeping men. The authors also found that disinhibited eating behaviour was highly prevalent among short sleepers.[255] Results from an epidemiological study[210] that assessed factors associated with sleep duration among 49,405 Australian adults aged 45 to 65 years showed that compared to 7 hours sleep, both short (<6 hours; OR 1.26, 95% CI 1.06 – 1.49) and long (≥9 hours; OR 1.72, 95% CI 1.57 – 1.89) sleep duration were associated with higher alcohol consumption. In the US, Krueger and colleagues[63] found that only short sleep duration was associated with higher risk for excessive alcohol consumption (OR 1.09, 95% CI 1.05 – 1.14). Findings from a similar study[230] among 4,411 Korean adults demonstrated that there was no significant association between alcohol consumption and sleep duration among these individuals.

It is difficult to explain the diversity among findings of these epidemiological studies, as the measures of alcohol consumption (including type, amount, frequency, and timing in relation to sleep) and also cut-points for sleep varies across these studies.

The biological explanation between effects of alcohol consumption on sleep is yet to be fully understood. It is hypothesised that alcohol dramatically reduces the action of glutamate (a common neurotransmitter) via its receptor which can lead to reduction in

the brain's activity.[255] Evidence indicates that there is a dose-response relationship between alcohol and the frequency of arousals during the second half of night-time sleep period.[256] The term "rebound effect" is generally used to describe second-half sleep disruption and it means that the sleep pattern and in particular length of REM sleep, alters with the initiation of alcohol metabolism and REM period gets even longer than normal once the alcohol is cleared from the bloodstream.[257] It has been consistently suggested that alcohol consumption could potentially alter the length of different sleep stages.[257]

2.6.2.2 Smoking

Although the earlier results from univariate logistic regression models showed that compared to never smoker, ever smokers had 25% (95% CI 1.07 – 1.51) increased risk of short (<6 hours) sleep duration, this association was no longer significant in the fully adjusted model. Data on the effect of smoking on sleep among older individuals are lacking. Results from epidemiological studies among younger populations[258-260] consistently indicate that cigarette smoking is associated with increased risk for poor sleep quality among men and women. In a large longitudinal population-based study, including 7,960 participants aged 12 to 18 years old at baseline, Patten and colleagues[258] investigated the factors related to sleep problems among these individuals. After a 5-year follow-up, findings showed that compared to non-smokers, established smokers had higher risk of developing sleep problems over the course of the study (OR 2.18, 95% CI 1.63–2.91). Similarly, Wetter and colleagues[259] in a study involving 3,516 adults (age ≥18 years) found that, compared to non-smokers, both male and female current smokers had an increased risk of developing insomnia symptoms compared to never smokers (males: OR 2.32, 95% CI 1.04 – 5.16, females: OR 1.88, 95% CI 1.09 – 3.23). In a cross-sectional analysis describing the association

between cigarette smoking and sleep disturbance, Phillips and colleagues[261] studied 484 individuals aged 14 to 84 years and found that habitual smokers are more likely to experience difficulties initiating sleep and maintaining sleep compared to non-smokers. Mak and colleagues[260] investigated the association between smoking and sleep problems among 29,397 Chinese students and reported that compared to never smokers, experimental smokers who smoked once or a few times had a higher risk of insomnia (OR 1.39, 95% CI 1.25 - 1.54).

There are several hypotheses on the effects of cigarette smoking on sleep patterns. It was previously found that habitual smokers tend to be single/unmarried, depressed and financially deprived compared to non-smokers[258] and it is well known that depression is an important risk factor for insomnia.[262] Similarly, medical conditions including pain, chronic chest diseases and obstructive sleep apnoea (OSA) may be more prevalent among smokers compared to non- and former smokers. Many of these medical conditions may also cause sleep problems.[260] Negative life events including death of a spouse, financial constraints, and marriage or work problem may trigger a causal pathway between smoking and insomnia.[263] Evidence indicates smokers with sleep problems are less likely to seek coping strategies other than cigarette smoking and therefore may be more susceptible develop further sleeping problems.[263] There are two biological effects associated with smoking (short- and long-term), which may negatively influence sleep. The short-term effects include regulation of certain neurotransmitters such as serotonin that is involved in the sleep-wake cycle regulation.[264] The long-term effects include frequent nocturnal awakening. During sleep, as a result of acute nicotine withdrawal, smokers, and in particular heavy smokers, may experience sleep fragmentation and frequent awakening.[264]

The present study did not find any significant association between sleep duration and smoking among the older Chinese people in GBCS. It is difficult to compare these findings with the current literature, since the majority of studies previously assessed the impact of smoking on sleep in younger individuals. The other possible explanation is that two important factors, duration and dose of smoking were not assessed in these studies. For example, if a person smokes a cigarette a day and another smokes a pack of cigarette, both would be similarly classified as current smokers. In current study, the comparison was between never smokers and ever smokers.

Future studies including more detailed analysis of smoking habits may be necessary to examine the relationship between smoking and sleep duration and quality. Additionally, a more detailed assessment of common sleep disorders such as obstructive sleep apnoea is required. Furthermore, it would be of interest to explore changes in sleep patterns in individuals undergoing smoking cessation programmes including a study of whether sleep duration has an impact on abstinence. In a recent randomised controlled trial, Okun and colleagues[265] assessed whether sleep disturbance during smoking cessation is associated with relapse among 322 women. The authors found there was no significant association between subjective sleep disturbance symptoms such as drowsiness with smoking relapse. In general, sleep disturbances are relatively prevalent among smokers[265] and future prospective studies are needed to examine whether such disturbances could predict the outcome of smoking cessation treatment.

2.6.2.3 Physical activity

In the present study, there was no significant association between physical activity levels and sleep duration. In line with this finding, Magee and colleagues[210] did not

find any association between moderate physical activity and sleep duration in 49,405 Australian adults aged 45 to 65 years. Similarly, Ryu and colleagues[230] also did not observe any significant association between sleep duration and physical activity levels among 4,411 Korean adults (age ≥19 years). In contrast, Krueger and Friedman[63] reported that an increase in the physical activity index was associated with lower risk of sleeping 9 hours or more among 110,441 adults (age ≥18 years) in the US (OR 0.90, 95% CI 0.87 – 0.93).

It has previously been shown that both short and long-term exercise is associated with increased slow wave sleep and total length of nocturnal sleep as well as improvement in sleep latency among healthy individuals.[216] Several studies have previously reported that increased physical activity may improve sleep among older adults. For example, Sherrill and colleagues[215] studied 722 adult men and women participants (mean age = 57 years) and found that regular activity, at least once a week, was associated with lower risk for difficulties maintaining sleep (OR 0.71, 95% CI 0.50 – 0.99) and also for any other sleep problems (OR 0.62, 95% CI 0.44 – 0.87). In another study, Merill and colleagues[216] assessed whether an intensive lifestyle modification programme (diet and physical activity) can reduce sleep problems among 2,624 individuals aged 30 to 80 years, and found that from baseline to the end the of 4 week intervention, the number of people with insomnia significantly reduced (-64%).

While a validated measure of general activity was used in the present study, more detailed assessment of physical activity including type, intensity, duration, and its relation to sleep timing maybe necessary to identify the relationship between physical activity and sleep. There are few studies describing the impact of physical activity on

sleep duration and there is a need for more randomised controlled trials.[216] This is particularly important given the prevalence of sleep problems in older individuals.

There are several hypotheses that explain how increased levels of physical activity could promote sleep including: thermoregulation and energy maintenance.[266] The regulation of body temperature is mainly controlled by the anterior hypothalamus. It has been found that a decline in body temperature as a result of increased peripheral skin blood flow plays an important role in sleep promotion in the evening.[219] It has been suggested that the thermogenic effect of increased physical activity prior to bed time may promote the onset of sleep.[267] It was reported that an exercise programme could potentially improve sleep impairment in vulnerable groups such as insomnia suffers and depressed individuals.[268]

2.6.3 Health-related conditions and sleep

2.6.3.1 Obesity

The current study found that compared to sleep duration of 7-8 hours, long (≥9 hours) sleep duration was associated with 45% (95% CI 1.16 – 1.15) increased risk of obesity in the whole sample. In stratified analysis, males aged 65 years and older, who slept 6-<7 hours and ≥9 hours had lower risk for being obese. Moreover, sleep duration of ≥9 hours was strongly associated with 45% (95% CI 1.16 – 1.80) higher risk of obesity among females. As discussed earlier in *Chapter 1*, numerous cross-sectional[3, 32, 48, 60, 116-118, 120, 121, 124, 125, 127, 131-134] and longitudinal[135-147, 149] studies, supported by systematic reviews[113] and meta-analyses,[114, 115] have previously investigated the possible link between sleep duration and obesity, but the findings of such studies have been mixed. The majority of current epidemiological studies suggest that short sleep duration[131, 135-138] is an important risk factor for obesity, while others have found that

sleep and obesity may interact in U-shaped manner,[3, 32, 121, 140-142] and some could not find any significant association between these two factors.[126, 145, 147] The present study used waist circumference to measure central obesity, while the majority of current studies on association between obesity have used BMI, which could explain these discrepant findings. Only a few studies examined the association between waist circumference and sleep duration in adults. In the Better Health for Better Hong Kong campaign,[120] involving 4,793 men and women with mean age of 42.4 years, central obesity was inversely associated with reduced sleeping hours in men (Regression coefficient (β) = -0.049, p = 0.014), in agreement with my data in men. In the Quebec family study, compared with adults reporting 7 to 8 hours of sleep, those with 5 to 6 hours of sleep had higher waist circumference (OR 1.69, 95% CI 1.15 – 2.39).[123] In contrast, sleep duration was not associated with abdominal obesity in sample of aged population (≥60 years) in Spain.[140] The relationship between sleep duration and waist circumference is very important, as it has been found that central adiposity has a strong correlation with metabolic variables such as insulin resistance compared to general obesity.[269]

In my study, short and long sleep duration was inversely associated with obesity in men. In women, the associations tended to be in the opposite direction, as long sleep duration was strongly associated with increased risk of obesity. The interpretation of these findings requires much caution, as gender differences have not been consistently reported in adults. It was previously found that sleep may have greater impact on body composition in women compared to men.[127] Sleep duration and sleep quality may be influenced by menopausal state.[270] It is also believed that menopause may also be associated with weight gain.[271] However, the underlying mechanisms for development of abdominal adiposity are complex and may include several other factors. Findings

from NHANES cohort[143] demonstrated that each additional increase hour of total nocturnal sleep duration was negatively associated with change in BMI among men and women aged younger than 50 years (premenopausal state for women). In a sample of Japanese adults (30 to 60 years), a U-shaped association was found between sleep duration (<5 hours, β 0.01, 95% CI 0.02 – 0.14 and ≥9 hours β 0.01, 95% CI 0.07 – 0.34) and BMI among men, but not among women. Results of a recent study by Theorell-Haglöw[127] among 400 women, aged 20 to 70 years showed that sleep duration was inversely associated with waist circumference (β = -1.22, p = 0.016). Impact of gender on sleep needs further investigation, as the current studies are mainly focused on men. Future studies are needed to investigate the hormonal response to sleep duration in men and women.

It is believed that chronic condition such as cardiovascular disease may disrupt sleep and induce unintended weight change.[272] As chronic conditions are relatively prevalent among older people, it may influence sleep-obesity association. It is generally established that short sleep duration is associated with obesity among younger people; several studies reported that such associations may diminish or disappear with increased age.[135, 143] Short sleep duration among older individuals could be due to underlying sleep disorders such as insomnia. Recently, Vgontzas and colleagues[150] reported that self-reported short sleep duration could be the result of the presence of emotional distress or presence of other underlying sleep problems rather than voluntary sleep restriction.

I found that long sleep duration was associated with increased risk of obesity in the whole sample. Long sleep duration may reflect poor quality sleep that may result in prolongation of time in bed. Similarly, short sleep duration could be secondary to sleep

disturbance. Thus, any interpretation of the impact of sleep duration on health should also take sleep quality into account. Unfortunately, it was not possible to determine quality of sleep in the GBCS cohort. Future studies using objective measures of sleep are needed to investigate the association between sleep duration and obesity among older individuals. These studies also need to control for underlying sleep problems such as insomnia and obstructive sleep apnoea.

2.6.3.2 Hypertension

In the fully adjusted model, compared to sleep duration of 7-8 hours, sleep duration of 6-<7 hours (OR 1.15, 95% CI 1.01 – 1.30) and 8-<9 hours (OR 1.14, 95% CI 1.01 – 1.29) were associated with higher risk of hypertension in the whole sample. In stratified analysis by gender and age, in older (≥65 years) males, hypertension was associated with sleep duration of 6-<7 hours (OR 1.55, 95% CI 1.05 – 29) and in younger females (<65 years) was associated with sleep duration of 8-<9 hours (OR 1.19, 95% CI 1.01 – 1.41). In line with this finding, previous studies also confirmed that there is a positive association between sleep duration and hypertension. Although there is a controversy between the findings of these studies, as some reporting that only short[38] or both short and long sleep duration[32] are associated with increased risk of hypertension. In contrast, a few studies[36] did not find any significant association between sleep duration and increased risk of hypertension. There are also only a few studies[33] highlighted the effect of gender and age on association between these two phenomena.

I investigated the association between sleep duration and hypertension among older Chinese people, and majority of the current studies have looked at the same association in younger population. In contrast with my findings, results from the Rotterdam study[36]

involving 5,058 older age participants, and study by Lopez-Garcia and colleagues[40] in 3,686 participants aged 60 and older showed that there was no association between sleep duration and hypertension among older individuals. I found that both short and long sleep duration may increase the risk of hypertension in the whole sample. In line with these findings, results from the Sleep Heart Health Study,[32] which involved 5,892 participants aged between 40 to 100 years showed that both short (OR 1.66, 95% CI 1.35 – 2.04) and long (OR 1.30, 95% CI 1.04 – 1.62) sleep duration were independently associated with increased risk of hypertension.

The current studies also highlighted the effect of gender on the association between sleep duration and hypertension. Data on the impact of gender is lacking and future studies are needed to support these findings. Recently Fang and colleagues[33] found that older women (≥65 years) who reported sleeping <6 hours a day had an increased risk of hypertension OR 1.44, 95% CI 1.16 – 1.80). Results from cross-sectional analysis by Cappuccio and colleagues[40] showed sleep duration was significantly associated with increased risk for hypertension only among females (OR 1.72, 95% CI 1.07 - 2.75). In another study, the association between sleep duration and hypertension was assessed both cross-sectionally and longitudinally among 10,308 British participants aged between 35 to 55 years old.[34] The findings of the cross-sectional analysis indicated that there was no significant association between sleep and hypertension in men. However women who were short sleepers (≤5 hours sleep per night) had higher risk for incidence of hypertension compared to those who reported sleeping 7 hours per night (OR 1.72, 95% CI 1.07 – 2.74).[34] In the longitudinal analysis, the significant association between short sleep duration and hypertension was attenuated following adjustment for cardiovascular (OR 1.42, 95% CI 0.94 – 2.16) and psychiatric co-morbidities (OR 1.31, 95% CI 0.65 – 2.63).[34] The underlying

mechanisms for the observed gender-specific association between sleep duration and hypertension in these studies are unknown. The majority of female participants in this study were menopausal, and it can be interpreted that hormonal changes as a result of menopause may also have an impact on their sleep patterns.[273]

The positive association between short sleep duration and hypertension may be attributed to sleep deprivation. It was previously found that sleep loss may have a negative impact on endocrine and metabolic function and also increase the activity of the sympathetic nervous system, and eventually result in hypertension.[274] Results from experimental studies showed that even after one night's sleep restriction (total sleeping time (3.6 to 4.5 hours), there were a significant increase in blood pressure in both normotensive[275] and hypertensive[43] individuals. Chronic sleep loss may lead to hypertension in the long run.[276] The increased risk of hypertension was also observed among long sleepers (≥9 hours). Although, the biological mechanisms underlying the impact of long sleep duration and hypertension is less well understood. It is believed that there may other factors may have influence the link between long sleep duration and hypertension. For example, results from the Nurses' Health Study[52] showed that weekly physical activity levels among women who reported sleeping 9 hours or more were 15% lower compared to women who slept 7 to 8 hours, suggesting that physical inactivity may increase the risk of hypertension. Moreover, poor sleep quality or underlying sleep problems may contribute to long sleep duration.[277]

In general, differences in geographical characteristics may have an influence on circadian rhythms among individuals.[278] For example, number of hours with sunlight is longer in Mediterranean countries, affecting work and leisure time.[38] Moreover, changes in sleep architecture due to ageing may be another explanation for observed

controversies among findings of studies investigating the association between sleep duration and hypertension. The studies that found a positive association between short sleep duration and hypertension were conducted in middle-aged participants,[32, 34, 38] and it can be argued that short sleep duration among these individuals may be mainly due to voluntary sleep restriction as a result of fixed schedules for getting up and going to work, whereas in older individuals who are mostly retired, short sleep may be due to underlying sleep disorders such as insomnia.[22]

2.6.3.3 Diabetes

There was no significant association between sleep duration and diabetes in the whole sample. However, in the stratified analysis, in female aged 65 years and older, compared to sleep duration of 7-8 hours, sleep duration of 6-<7 hours was associated with 55% (95% CI 1.07 – 2.24) increased risk for diabetes. Several other epidemiological studies[45-52, 54-60] have previously examined a potential link between sleep duration and diabetes, but their findings are inconsistent. Some studies have observed a U-shaped[48, 49, 56, 57, 279] association between sleep duration and diabetes, while some studies found either short[45-47] or long[52] sleep duration to be risk factors for prediction of diabetes. Additionally, several have reported no associations.[51, 60]

In line with current findings, results from the Nurses' Health study[52] also showed that both short and long sleep duration were associated with type 2 diabetes; however after full adjustment for potential confounders, only long (≥9 hours per night) sleep duration was strong predictor for incidence of diabetes (HR 1.29, 95% CI 1.05 – 1.59). In another study, Tuomilehto and colleagues[50] found that compared to 7 hours sleep duration, short (≤6 hours; OR 2.55, 95% CI 1.21 – 5.35), and long (≥8 hours; OR 1.76, 95% CI 1.12 – 2.61) sleep duration were associated with higher risk for type 2 diabetes

among middle-aged women but not men. The findings from the current study showed that short sleep duration was associated with diabetes among women who were aged 65 years and older.

It is difficult to compare the results of my study with findings from other studies, as the majority of these studies have been conducted among middle-aged and younger participants. Epidemiological data on the association between sleep duration and diabetes among older Chinese adults is also lacking and the effect of gender on such associations has not been fully explored. Overall, current epidemiological studies on the association between sleep duration and diabetes have used subjective sleep measures (i.e. self-reported questionnaire), which may introduce some potential biases. Knutson and colleagues[51] studied 670 men and women aged 18 to 30 years and they using objective measures of sleep (actigraphy) and they did not find any significant association between sleep duration and diabetes. Future studies using objective measures of sleep (i.e. actigraphy, polysomnography) are needed to assess the link between sleep duration and risk of diabetes in older people.

There are several biological mechanisms that could explain the link between sleep duration and diabetes. Sleep deprivation may result in higher secretion of cortisol, a counter regulatory hormone, which could potentially promote insulin resistance.[66] An increase in sympathetic tone also has been observed following sleep restriction, which would negatively influence pancreatic function, leading to glucose intolerance.[66] It has also been hypothesised that sleep restriction may also lead to diabetes through its effect on weight gain and alteration in regulation hormones such as leptin.[52]

2.6.4 Clinical implications

As stated earlier, sleeping shorter or longer than the average level (usually 7-8 hours per night) has been associated with greater risk for health and well-being.[3] Previous studies carried out in Western countries have reported that factors including age, gender, income level, education level, smoking, alcohol consumption, physical activity, hypertension, obesity, diabetes are associated with sleep duration.[63, 210] Findings of the current study among older Chinese confirm some of these observations, but highlight the complexities of the relationships, and potential roles for gender and age in determining the associations between sleep and the various factors examined.

Although the results did not demonstrate any significant association between lifestyle factors (smoking, alcohol consumption, and physical activity level) and sleep duration, current evidence suggest that changes in lifestyle routine such as increased physical activity levels may be beneficial for sleep improvement.[215, 216] However, there is a need for well-designed future studies to assess the effectiveness of lifestyle modification on sleep among older individuals. Recently, in a randomised controlled study, Alessi and colleagues[280] evaluated the effectiveness of a non-pharmacological interventions on the sleep patterns of older individuals in nursing homes. The intervention involved: a reduction of time spending in bed, increased sunlight exposure, increased physical activity, reduction in night-time noise, and structured nocturnal bedtime. Their findings demonstrated that the intervention resulted in significantly reduced daytime sleepiness and increased engagement in social activities. Data on the effect of other lifestyle modification such as smoking and alcohol consumption are lacking, although it was previously reported that smoking cessation could improve sleep.[281] Lifestyle

interventions may perhaps have to be employed at an earlier age to have a beneficial effect.

2.6.5 Strength and limitations

The current study has some strengths and limitations. It benefits from a large sample of fairly well characterised individuals that provide higher statistical power to allow exploration of a range of factors that were potentially associated with short and long sleep durations while addressing a number of potential confounders. While in the current analysis, I have controlled for different confounders, it should be taken into account that there may be other confounders that were not measured. One of the main limitations of the present study was that the effect of obstructive sleep apnoea (OSA), as a potential confounder was not assessed nor other surrogate markers of OSA. Using validated and reliable questionnaires such as Berlin questionnaire,[282] Epworth Sleepiness Scale (ESS)[31] or even simple single question "Do you snore in your sleep?" would be useful to capture such data. Collection of such data would also enable categorisation of participants into either low or high risk of OSA based on reported snoring and for a higher ESS score. Comparing results of the stratified (high risk of OSA vs. low risk of OSA) analyses on the association between sleep duration obesity, hypertension, and diabetes would provide insight as to whether the associations remain and thus independent of OSA. Categorisation based on the combination of short sleep duration and OSA can be used to assess their joint effects. For instance, results of a very recent study[283] in 838 community participants age 40-69 years in Korea showed that combination of OSA and short sleep (<5 hours) duration increased the risk of visceral obesity (OR 4.40, 95% CI 1.80, 10.77).

Moreover, the uniqueness of social and cultural characteristics of participants and also setting of the study would limit the generalisability and comparison of the results with many studies that have been carried out in Western populations.

A major limitation of the study is its cross-sectional design that means the temporal sequence of the association between sleep duration and hypertension, obesity and diabetes is unclear and thus causality cannot be inferred. Additionally, there is a risk of reverse causality in cross-sectional studies. Findings of this study on the impact of gender on association between sleep duration, obesity, hypertension, and diabetes needs to be interpreted cautiously, as the role of chance needs to be considered while drawing conclusions. Using a multi-comparison correction could render some of the findings statistically insignificant. Future longitudinal studies are needed to further examine such associations among older individuals and also explore the impact of gender. There is a concern that the sample may not totally be representative of the older population in China as a result of the recruitment method. Nevertheless, the chance of selection bias is low because the membership was open to anyone and individuals have been chosen randomly for inclusion into the study. While some studies[29] collect objective sleep data, it is not practical to utilise these labour and time-consuming methods (actigraphy and polysomnography) to collect data from such a large sample. Because of data collection across a broad range of factors, it was not possible to collect detailed information regarding individual factors. This makes it difficult to study the relationship between sleep and these factors in detail and may miss subtle relationships that could, over time, have significant implications. The present study reports some interesting findings that need to be explored with more specific studies that include more detailed data collection.

2.6.6 Key points

Both short and long sleep duration may have adverse health outcomes. Short sleep duration is relatively prevalent among this older Chinese population in the GBCS. I found that females, older age, being widowed, lower education level, and lower income level were strongly associated with short sleep duration, while hypertension was strongly associated with long sleep duration. There was an inverse association between short and long sleep duration and obesity among males aged 65 years and older. In females, long sleep duration was association with hypertension and obesity only among those who were younger (<65 years), and short sleep duration was associated with diabetes among those who were older (≥65 years). Further more detailed prospective study with objective measures of sleep (quantity and quality), including consideration of sleep disorders, is required to fully determine the various factors (also assessed objectively) associated with sleep and its impact on health.

3 THE COMPLEX ASSOCIATIONS AMONG SLEEP QUALITY, ANXIETY-DEPRESSION, AND QUALITY OF LIFE IN PATIENTS WITH EXTREME OBESITY

3.1 Abstract

Introduction: Sleep duration and quality have been associated with obesity. Sleep disturbance has been reported to be associated with stress and depression among non-obese populations, but these relationships have not been previously examined in the extreme obese population. The objective of the present study was to examine the complex associations among sleep disturbance, quality of life, anxiety and depression in a patient sample with extreme obesity.

Methods: Two hundred and seventy consecutively recruited patients with a mean body mass index (BMI) of 47.0 Kg/m^2 were studied. The correlation coefficient, multiple linear regression, and structural equation model (SEM) analysis were utilised to evaluate the association between the Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS), Impact of Weight on Quality of Life-Lite (IWQOL-Lite) and Hospital Anxiety and Depression Scale (HADS).

Results: The mean (standard deviation; SD) PSQI score was 8.59 (5.11), and mean ESS score was 8.84 (5.79). After controlling for potential confounders, poor sleep quality and excessive daytime sleepiness were found to be significantly associated with all the components of IWQOL-Lite; physical function (β = -0.32, β = -0.27; $p<0.01$), self-esteem (β = -0.23, β = -0.30; $p<0.05$), sexual-life (β = -0.30, β = -0.35; $p<0.05$), public distress (β = -0.39, β = -0.39; $p<0.01$), and work (β = -0.26, β = -0.48; $p<0.01$). It was also found that the PSQI global score had a positive significant

association with anxiety (β = 0.29; p = 0.01) and depression (β = 0.31; p = 0.01) components of HADS**.**

Conclusion: Poor sleep quality was strongly associated with mood disturbance and poor quality of life among extreme obese patients. Future interventions are needed to address sleep disturbance to prevent the further development of psychological co-morbidity and potentially worsening of obesity among these individuals.

3.2 Introduction

Obesity is a major public health problem. To prevent and manage severe obesity, there is a need for greater understanding of factors that could contribute to the development and perpetuation of obesity in this clinically challenging population. Recently, there has been great interest in the role of both sleep duration and quality in the onset and progression of obesity.[114] The associations among sleep duration, sleep quality, and obesity are bidirectional. Once obesity occurs, sleep is likely to be disturbed, and weight loss has been observed to reduce sleep disturbance and obesity-associated sleep-disordered breathing.[168]

Apart from the relationship with obesity, sleep duration and quality are related to other health outcomes including psychological problems.[284] A number of studies have reported bidirectional relationships between sleep and depression with some suggesting that sleep quality may initiate and/or exacerbate mood disturbance, and that by improving sleep, it may be possible to improve mood.[284] The majority of studies examining a link between sleep and depression, and quality of life, however, have focused on the non-obese population.[285] In obese individuals, depression could hinder weight loss and its maintenance. Price and colleagues[286] have reported that depressive symptoms could potentially predict weight regain among overweight individuals who are successful with initial weight loss.[286] Currently, the potential role of sleep in health and wellbeing of individuals with severe obesity is underappreciated. An understanding of the interrelationships between sleep, mood and quality of life could inform a more tailored approach to the prevention and management of severe obesity.

3.2.1 Sleep as a potential risk factor for obesity

Based on the limited data available, average total sleep duration appears to have decreased compared to previous decades. In the US, the results of the comparison of total nocturnal sleep duration in year 2009 vs. year 1969 demonstrated that there has been a reduction of sleep by 1 hour and forty minutes.[3] The number of people who reported short sleep duration (≤6 hours of sleep per night) also increased in 2004 compared to 1985 (Figure 3-1).[287] It has been estimated that 43% of the younger population who aged 30 to 44 years consistently report that they sleep 7 hour or less per night.[3] It appears that some features of modern society such as computers and the internet have a strong influence on shortening sleep duration over time.[287]

Evidence describing the association between sleep and obesity has been fully discussed in *Chapter 1*. The results of the studies that evaluated the association between sleep and weigh gain are controversial. For instance, in the Wisconsin Sleep Cohort Study (WSCS), a U-shaped association was detected between sleep duration and BMI.[121] In a similar study, Tamakoshi and colleagues[116] found that only short sleep duration was significantly associated with obesity among 104,010 Japanese men and women. Magee and colleagues[133] reported that the positive association between sleep and BMI was only observed in individuals who were younger than 65 years old. In contrast, a few studies[146, 147] did not find an association between sleep and excessive weight gain. To date, longitudinal studies across different populations (e.g. different sleep and age categories) in various countries consistently reported that short sleep duration is a strong predictor of obesity.[136-139] In a recent meta-analysis, Cappuccio and colleagues[114] systematically reviewed population-based studies and quantified the risk of short sleep duration (<10 hours per night for children and <5 hours per night

for adults) in onset of obesity. They found that a 1 hour reduction of total time of sleep per 24-hours could potentially predict a 0.35 kg/m^2 increase in BMI in adults.

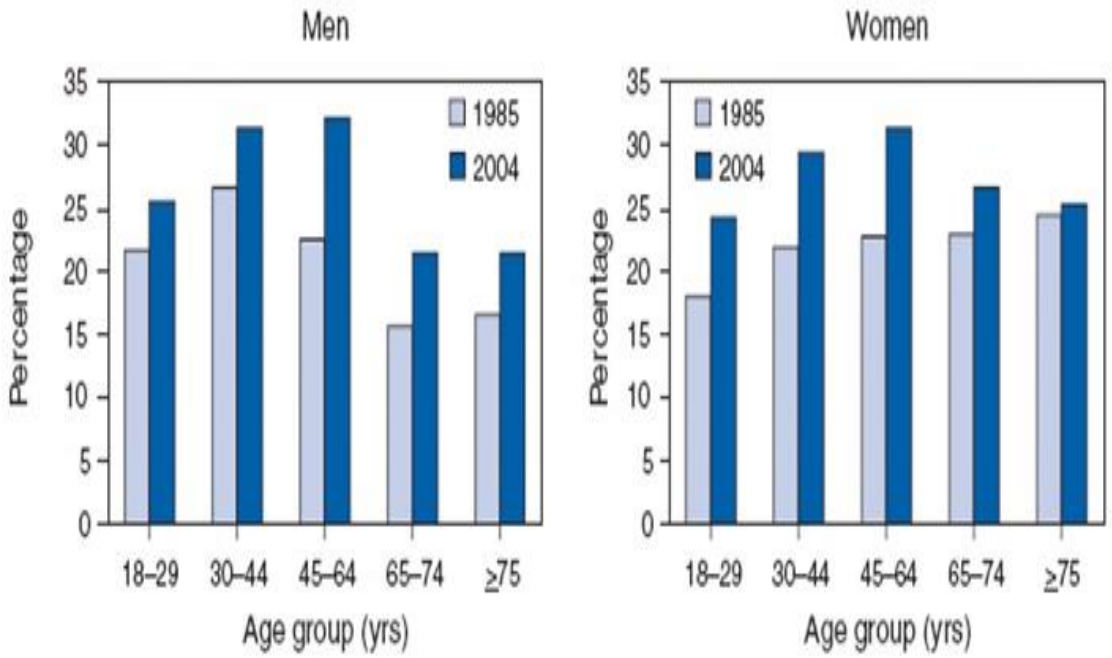

Figure 3-1. Percentage of sleep deprived individuals (average of ≤6 hours of sleep per night), by gender and age, 1985 and 2004, United States.[287]

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3.2.1.1 How does sleep relate to obesity?

Some of the current potential mechanisms underlying association between sleep and obesity were fully discussed in *Chapter 1*.

Sleep loss could potentially increase the activity of the sympathetic nervous system, which may affect food intake through disruption of the regulation of appetite hormones such as leptin and ghrelin.[178] Sleep deprived individuals may also have a higher appetite for foods containing higher amount of fat, sugar and carbohydrate.[190]

Furhtermore, as a result of fatigue and daytime sleepiness they are more likely to be engaged in sedentary behaviours[175] and consequently have reduced. Finally, disruption in circadian rhythm may also disrupt metabolism and affect appetite and food intake and increase the risk of obesity.[178, 198-200] Each aspect may promote the opportunity for obesity development over time

3.2.2 The intimate relationship between sleep and depression

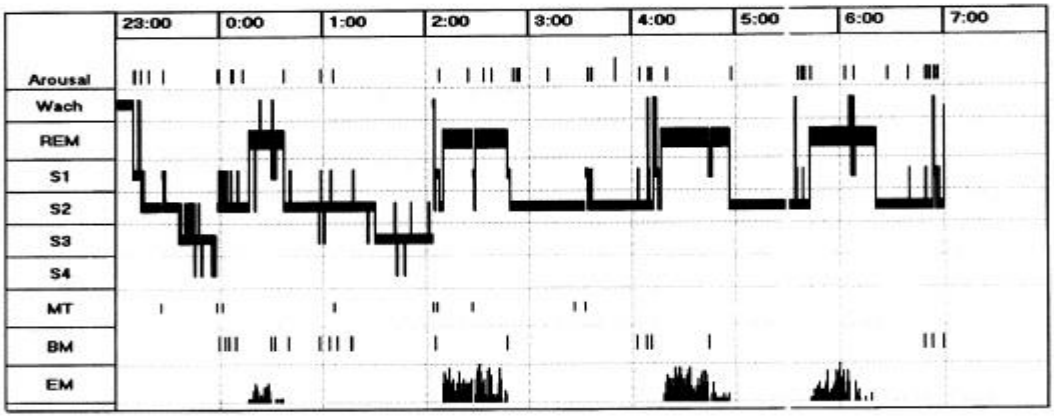
Depression results from an interaction between genetic, biological, and environmental factors.[244] It has been previously found that lack of sleep was associated with mood disorders.[203] It is unclear whether sleep is a predictor of depressive symptoms or sleep problems are the outcome of depression. It is believed that there is a bi-directional link between sleep difficulties and depressive psychopathology.[244] Depressed individuals are more likely to complain about their sleep. On the other hand, sleep disturbances may be attributable to increased risk for the incidence and development of depression over time.[244]

The results from experimental studies[288, 289] demonstrated that sleep restriction may potentially increase depressive symptoms among healthy participants. For instance, Kahn-Greene and colleagues[289] collected data using Personality Assessment Inventory (PAI) from 25 healthy adults and found that means and standard deviations for selected PAI subscales for cognitive (Baseline mean (SD): 44.7 (7.1) vs. Sleep deprived mean (SD): 48.3 (8.3)) and affective (Baseline mean (SD): 45.3 (5.3) vs. Sleep deprived mean (SD): 48.8 (7.3)) aspects of depressive symptoms significantly differed between baseline and following of 65 hours sleep deprivation among these individuals.[289] No change was detected in the physiological component of depressive symptoms, but the

overall scores were found to be clinically higher once the sleep deprivation period terminated.

Electroencephalograph (EEG) sleep studies have shown that a reduction of slow wave sleep (SWS) as a result of a reduction in the time gap between commencement of sleep and onset of first rapid eye movement (REM) episode has been observed in EEG records of depressed individuals.[290] The sleep patterns of these individuals were also characterised by an increased amount of eye movement, prolonged REM sleep, and a delay of onset of first REM episode (Figure 3-2).[291] It is postulated that a decrease in the length of REM periods plays an important role in the incidence of depression. However, the above hypothesis is yet to be confirmed as there are some potential factors such as age and gender that broadly influence sleep.[292] It is of interest that treatment with antidepressants is associated with suppression of REM sleep. It has been found that the length of SWS also decreases as age increases. Data describing the effect of gender on sleep are limited. Compared to depressed women, reduced SWS were found in depressed men.[292]

Healthy control



Depressed patient

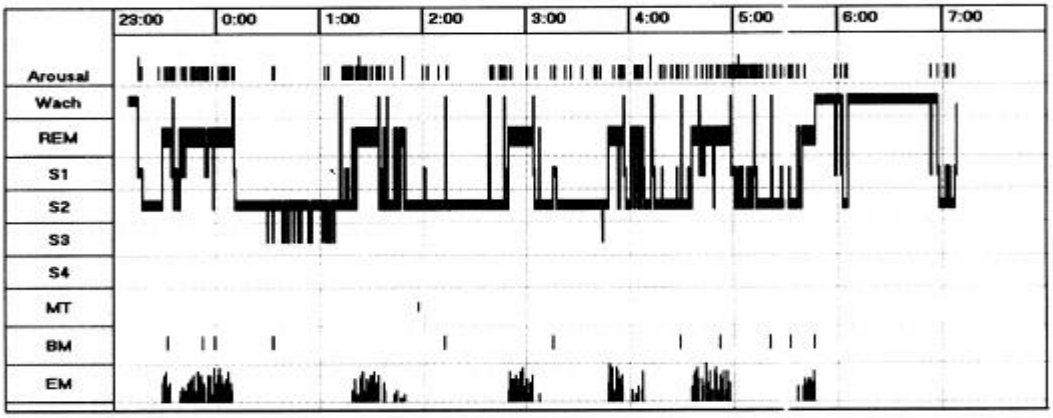


Figure 3-2. A comparison between sleep profiles of a medication-free depressed female with a healthy female control. Wake (*W*), Rapid Eye Movement (*REM*), S1-4 (*Sleep stages 1-4*), Movement Time (*MT*), Body Movements (*BM*), Eye Movements (*EM*).[291]

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Epidemiological evidence suggests that sleep problems, such as insomnia, which is defined as difficulty initiating sleep and maintaining sleep, are associated with a higher risk of developing depression. Insomnia patients often face prolonged and disappointment at not being able to sleep, which can lead to hopelessness, a preliminary trigger for depression.[293] A large number of longitudinal studies with either short or long follow-up periods have investigated the role of insomnia in the

prediction of depression over time.[293-298] The results from these studies have been controversial, in terms of reporting the odds ratio for measuring the association between insomnia and depression. For example, in 1989, Ford and Kamerow[297] reported that risk of developing major depression symptoms was much higher among individuals with insomnia compared to those without insomnia (Odds Ratio (OR) 39.80, 95% CI 19.8 - 80.0) with a very large OR and wide confidence interval indicating a lack of precision,[297] while another study by Neckelmann and colleagues[296] in 2007, reported no association (OR 1.10, 95% CI 0.80 - 1.60)[296] The observed controversy across the studies might be due to the fact that each study defined insomnia differently, as the majority of studies that had been published after 2001, defined insomnia on the basis of difficulty initiating sleep, difficulty maintaining sleep and daytime consequences of insomnia, which indicated that the conceptualisation of insomnia had changed dramatically over the past 20 years. Additionally, the observed controversy might be explained by different in population characteristics, population size, and length of follow-up. It is almost impossible to differentiate whether the clinical symptoms of insomnia per se trigger depressive symptoms or the poor sleep quality as the result of insomnia is the predictor of depression.

A recent meta-analysis of 21 longitudinal studies[299] quantitatively investigated the impact of insomnia in the prediction of depression. The findings indicated that compared to people with no sleep difficulties, non-depressed people with insomnia have a two-fold increased risk (OR 2.10, 95% CI 1.86 - 2.38) of developing depression. One the major features of insomnia is excessive daytime sleepiness. It has been reported that fatigue and daytime sleepiness are highly correlated with both depression and anxiety.[244] Excessive daytime sleepiness has a negative impact on daily functioning and work performance.[299]

3.2.2.1 How does sleep relate to depression?

The exact underlying pathophysiology of sleep and promotion of depression is not known. It has been suggested that the prefrontal cortex (PFC) and the serotonergic system play an important role in regulation in sleep-wake cycle that might be associated with depression.

3.2.2.1.1 Prefrontal cortex (PFC)

It is hypothesised that co-occurrence of sleep interruption and depression take place in the PFC. Studies that previously evaluated metabolic regulation in the PFC indicated that metabolic activity levels may also have an impact in synchronisation of the sleep/wake cycle.[300] Activation of the PFC is associated with wakefulness, while deactivation of the PFC could potentially induce sleep.[301] Increased need to sleep during the daytime as a result of obtaining insufficient sleep at night has been found to be associated with a decrease in activity levels in the PFC, which support the hypothesis that impairment of the PFC affects mood regulation and can lead to development of depression.[300]

3.2.2.1.2 Serotonergic system

Another possible mechanism that may link sleep to affective disorders such as depression is an alteration in the functionality of serotonin, a neurotransmitter that decreases during nocturnal sleep and has been found to play an important role in depression.[302, 303] In depressed individuals, the sensitivity of serotonin receptor 1A has been found to be dramatically decreased, therefore it was hypothesised that sleep restriction might also be associated with desensitisation of the serotonin receptor.[303] Roman and colleagues,[303] examined whether there is a link between chronic sleep restriction and desensitisation of serotonin receptor 1A receptor system in rats. They

found that chronic sleep loss was significantly associated with desensitisation receptor 1A, and receptor sensitivity was still not back to normal during sleep recovery.[303] Chronic sleep loss, which is highly prevalent among individuals with insomnia, may increase their susceptibility to develop depression over the longer term.[299]

Additional evidence from animal[304, 305] and human studies[306, 307] postulated that the short allele of the serotonin transporter gene is associated with both insomnia and depression. It has been highlighted that the presence of short allele may have a negative impact on sleep and increase the risk for onset and progression of depression.[89] While the result of such studies support the hypothesis for an existing relationship between sleep disturbance, serotonin and depression, these relationships were examined only in small samples.[306]

3.2.3 Effects of antidepressant treatment on sleep

Selective serotonin reuptake inhibitors (SSRIs) are widely used to treat psychiatric disorders such as depression.[308] It is well-known that the majority of depressed individuals suffer from sleep problems.[299] Interestingly, insomnia appears to be an important symptom that most of patients with depression would seek medical treatment for, and it has been previously found that alleviation of sleep disturbance in depressed individuals was associated with higher adherence to psychological treatments.[309] It was stated early on in this chapter that the sleep architecture of individuals with depression is more likely to be disrupted. Evidence indicates that anti-depressants may have a therapeutic effect on the sleep profile of these individuals.[308] The majority of the current literature[310] only assessed the acute effects of SSRIs on sleep and data on their chronic effects are lacking. Effects on REM sleep (reduction in

total amount of REM and delay of first entry into REM) have been reported by several controlled studies[311, 312] on effects of SSRIs on sleep.

3.2.4 Sleep as a risk factor for impaired quality of life

Quality of life (QoL) and health-related quality of life (HRQoL) are defined as a personal perception of an individuals' non-medical health and well-being.[313] The concept of QoL cannot be driven from a single factor, whereas the interaction of several factors is required to reflect one's satisfaction of different dimensions of life including; physical, social and mental well-being.[314] It is also believed that perception of QoL may go beyond complete physical and mental health, although the exact definition is not known yet.[315] The final estimation of QoL can only be declared by the individual him/herself, which has been found to be influenced by certain factors such as age, gender, social and socio-economic status.[316] Sufficient sleep is necessary for physical and emotional wellbeing. Moreover, poor sleep may negatively affect one's well-being and quality of life.[317] Prolonged sleep deprivation has been found to be associated with lack of concentration, and social dysfunction.[317] Daytime sleepiness as a result of chronic sleep problems has been found to have a negative impact on job satisfaction.[318] Sleep disturbance, and particularly daytime sleepiness, can result in low energy levels, which could be a potential marker for impaired physical function of HRQoL. Sleep restriction triggers sympathetic nervous system activity and a rise in cortisol secretion i.e. a stress state.[66] Sleep loss is also associated with impaired immune response and metabolic changes.[319] These effects, in turn, could have an impact on physical and mental well-being, and hence quality of life. Sleep deprived individuals may experience a decline in cognitive function and mood instability which could potentially contribute to HRQoL impairment among these individuals.[318]

In a recent cohort study, Faubel and colleagues[317] investigated the possible effect of sleep duration on quality of life in 3,834 young and middle-aged persons. Their results indicated that women who reported short (≤5 hours per night) or long sleep duration (≥10 hours per night) were more likely to report worse scores on the physical (≤5 hours sleep per night: Beta regression coefficient (β) −7.15, 95% CI −11.12 - −3.18, ≥10 hours sleep per night: β −6.38, 95% CI −9.96 - −2.80) and mental (≤5 hours sleep per night: β −3.53, 95% CI −6.79 - −0.26, ≥10 hours sleep per night: β −0.98, 95% CI −3.92 - 1.97) component of short-form health survey-36 (SF-36) compared to those who reported sleeping 7 hours. They also reported that men with short sleep duration (≤5 hours per night) had lower scores on the physical dimension.

Briones and colleagues[320] assessed the link between sleepiness and general health status in a cross-sectional sample of 129 individuals aged between 25 to 65 years. Their result demonstrated that sleepiness is inversely correlated with different components of quality of life including; "general health perceptions" ($r = -0.30$, $p<0.05$), "energy/fatigue" ($r = -0.41$, $p<0.05$), and "role limitations due to emotional problems" ($r = -0.30$, $p<0.05$). The score of Multiple Sleep Latency Test (MSLT) was also inversely associated with "energy/fatigue" ($r = -0.19$; $p<0.05$). The authors controlled the analysis for some potential confounders such as chronic illness and BMI.[320]

Medical and psychosocial stressors are prevalent among patients with insomnia. Vallieres and colleagues[316] recently reported that death of loved ones, divorce, illness, and unemployment are common causes for short-term insomnia and that underlying stress could negatively affect an individual's quality of life.

Quality of life among individuals suffering sleep problems could significantly be affected by overall impairment in physical and mental well-being.[318] Disrupted sleep

may lead to significant impairment in both social and work areas due to a decrease in work productivity, reduced cognition function, and increased morbidities.[318]

3.2.5 Rationale for assessment of the interactions between sleep quality, depression, and quality of life among extreme obese individuals

To my knowledge, no study has examined the interactions among sleep and psychological and quality life issues in extreme obese patients, an increasingly challenging clinical population. The current literature that evaluated the association between poor sleep and depression and also between poor sleep and quality of life mainly concentrated on associations in non-obese populations and across different age group with various health conditions including hemodialysis,[321] cancer,[322] heart diseases,[323] Parkinson's disease,[324] and type 2 diabetes mellitus.[325]

A growing body of epidemiological evidence indicates that both sleep quantity and quality are associated with increased risk of obesity among men and women.[326] It is also known that sleep has an important role in development of depression. Therefore, it is necessary to have a greater understanding of obesity and its psychological co-morbidities. Recognition and addressing sleep problems among obese individuals is necessary as sleep improvement interventions may thus improve mental health and prevent worsening of obesity per se among this population.

3.3 Aim and study questions

To estimate the prevalence of mood disturbance, sleep disturbance and quality of life among extreme obese individuals.

The study questions included:

- Are there any associations between sleep disturbance and anxiety and depression levels among this population?
- Is there any association between sleep disturbance and quality of life among this population?
- How are sleep disturbance, depression, quality of life, and obesity-related conditions associated in a single structural equation model (SEM)?

3.4 Methods

3.4.1 Study population

A retrospective analysis of data collected as part of the evaluation of a regional specialist weight management service was carried out. The patients attended community-based clinics in the South Birmingham Primary Care Trust (PCT) catchment area. Clinics were held in large general practices in the area. Patients were referred to the service by their general practitioner using a standardised proforma. Two hundred and seventy adult patients (aged 17 to 80 years) consecutively enrolled into the service from January 2009 to October 2011 were included. The number of participants included was comparable to other studies of this patient population.[321, 327, 328] Criteria for enrolment were BMI ≥35 kg/m^2 with a co-morbidity (e.g. diabetes mellitus) or BMI ≥40 kg/m^2 without a co-morbidity, based on recommended criteria from the UK National Institute for Health and Clinical Excellence guidance (NICE CG43).[329] There was also a requirement for patients to have previously attended other weight management services (commercial/community/primary care) without success. Self-reported questionnaires assessing sleep, anxiety-depression, and quality of life were collected at the first visit where detailed clinical information and anthropometric measures were collected from all patients. The study was done as part of service evaluation and examined anonymised data; therefore no formal ethical approval was needed.[52]

3.4.2 Data collection

Data collected included demographic information, height, weight, BMI, blood pressure, obesity co-morbidities, and questionnaire information (described below).

The service administrators collected demographic data while trained physicians with a specialist interest in weight management collected the clinical data. Questionnaires were mailed to patients prior to their first appointment and were collected at the first appointment. The validated questionnaires were selected by the specialist weight management service as part of their comprehensive patient assessment and in line with recent recommendations.[330] All data was input into a secure NHS database with anonymised data used in the analyses.

Sleep disturbance was assessed using the Pittsburgh Sleep Quality Index (PSQI)[30] and daytime sleepiness using the Epworth Sleepiness Scale (ESS).[31] Mood was assessed using the Hospital Anxiety and Depression Scale (HADS),[331] and quality of life was assessed using Impact of Weight on Quality of Life-Lite (IWQOL-Lite).[332] All questionnaires are shown in Appendices.

3.4.2.1 Sleep disturbance

Sleep quality and sleep disturbance were assessed using the PSQI, a validated self-rated questionnaire that assesses sleep problems in seven aspects including sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance use of sleep medications, and daytime dysfunction.[30] A global score ranging from 0 to 21 is generated from the sum of the component scores. Individuals with total PSQI scores of ≥5 are identified as having severe sleep problems.[30] Daytime sleepiness was also assessed using ESS, a validated self-report questionnaire with the maximum score of 24. It consists of eight questions with a 4-point scale, which asks participants to rank the chance of dozing off in different situations (e.g. sitting and reading; as a passenger in a car for an hour without a break). The higher the scores indicates the greater daytime sleepiness.[31]

3.4.2.2 Mood

Mood (anxiety, depression) was assessed using HADS, a fourteen-item questionnaire that has been developed to screen non-psychiatric patients.[331] It consists of two subscales; anxiety subscale (HADS-A) and depression subscale (HADS-D) each including seven items. Each item is measured on a 4-point Likert scale, each ranging from 0 to 3, resulting in a maximum score of 21. A score above seven on each subscale implies the presence of potential distress. The following cut-points were used to categorise the participants: 0–7 (non-case), 8–10 (borderline case), ≥11 (case).[331]

3.4.2.3 Quality of life

Quality of life was assessed using the weight specific IWQOL-Lite, a 31-item self-rated questionnaire.[332] It measures weight-related quality of life in five areas; physical function, self-esteem, sexual life, public distress, work and a total score. Each component was measured on a five-point scale, ranging from 1 to 5 (from "never true" to "always true"). The total score ranges from 0 to 100, with a higher score indicating better health-related quality of life.[332]

3.4.3 Statistical Analysis

Data were analysed using the SPSS Version 18.0 (SPSS, Inc., Chicago, IL). Pearson correlation coefficients were used to assess the associations between questionnaire scores. Linear regression model was used for data analysis. For using regression model, I assumed that the responses are continuous, and they are normally distributed, the linearity assumption was visually assessed between independent variables (ESS scores and PSQI scores) and outcomes of interest (IWQOL-Lite scores and HADS scores), using scatter plot. In addition, using HADS and IWQOL-Lite scores as dependant variables in regression model, I also assumed that "distance" between

categories are equal. In previous studies that were assessing similar trend, the multiple regression was employed to assess such associations. For example, Havlikova and colleagues[324] have previously examined the relationship between sleep disturbances (measured using the Epworth Sleepiness Scale (ESS), and the Pittsburgh Sleep Quality Index (PSQI)) and quality of life (measured using the Parkinson's Disease Quality of Life Questionnaire (PDQ-39) and depression and anxiety (measured using, the Hospital Anxiety and Depression Scale (HADS)), among 93 Parkinson's disease patients. Their findings showed that after adjustment for age, gender and disease duration, PSQI (β 0.30, $p<0.001$) and anxiety was significantly associated with quality of life scores (β 0.29, $p<0.001$) among these patients. In another study, Martin and colleagues[333] used multiple regression to assess the association between sleep disturbance (measured using the Pittsburgh Sleep Quality Index (PSQI), and quality of life (measured using the Medical Outcomes Study 12-item Short Form Survey Mental Component Summary score), and depressive symptoms (measured using the five-item Geriatric Depression Scale) over 3 and 6 month follow-up of 121 older adults living in assisted living facilities (ALFs). Their findings showed that more self-reported sleep disturbance at baseline was associated with worse health-related quality of life (β(SE) 0.01(0.004), $p = 0.01$) and worse depressive symptoms (β(SE) 0.06 (0.02), $p = 0.002$).

Associations between HADS-A and HADS-D and components of PSQI and ESS were assessed using multiple linear regression. Moreover the association between PSQI Global score and ESS total score with components of IWQOL-Lite (physical function, self-esteem, sexual life, public distress and work) were assessed using multiple linear regression. In the analyses, the score of dozing off in the situation "car in traffic" was omitted, because this question is commonly answered in the negative by patients

because of concerns about driving licences. The multiple linear regression was adjusted for age, gender, hypertension, diabetes, and obstructive sleep apnoea (OSA). Linear regression analysis, analysis of covariance and factors analysis are widely used to examine the association between predictor variables and outcome of interest, but they do not necessarily provide an explanation of how variables relate to one another. Structural Equation Modelling (SEM) is one of the methodological tools that are being recently used to overcome this problem.[334] I used SEM to determine whether our hypothesised model is valid. The associations between *poor sleep factors* (PSQI and ESS) and *obesity-related conditions* (diabetes, hypertension and OSA) in predicting HADS-D and IWQOL-Lite total score based on the proposed theoretical model using statistical package SPSS/AMOS (student version 5). I removed one of the question of PSQI "During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?" due to the similarity with one of the HADS questions "I have lost interest in things, *definitely, sometimes, not much, not at all*". *Poor sleep factors* latent was defined by two variables; ESS score and modified score of PSQI, and *obesity-related Conditions* was defined by three variables; hypertension, diabetes and OSA. The total score of IWQOL-Lite and HADS depression score were assessed by the both latent (endogenous factors). Maximum Likelihood (ML) estimation approach[335] was applied for the models with an interaction terms, which included a latent variable. A bootstrap method was utilised to investigate the direct, indirect and total effects.[336] The advantage of bootstrapping is that it can create accurate standard errors that are independent of any assumptions for a normal distribution of data, which is required for calculation of regression weight by AMOS/SEM. It can also provide the probability levels for direct, indirect and total effect.[336] Five fit indices were used to assess the adequacy of model fit; 1) The

comparative fit index (CFI) >0.90, 2) Goodness-of-fit statistic (GFI) >0.95, 3) Adjusted goodness-of-fit statistic (AGFI) >0.90, 4) standardised root mean square residual (SRMR) <0.08, 5) Root mean square error of approximation (RMSEA) <0.05 and the upper bound of its 90% confidence interval <1 values indicate a good fit.[334] A two-tailed test were used throughout and a p-value of <0.05 was considered statistically significant.

3.5 Results

A total of 270 patients (202 female) were enrolled. The descriptive characteristics of the participants are presented in Table 3-1. The mean (standard deviation; SD) age was 43.3 (12.6) years. The mean BMI was 46.9 (7.8) kg/m^2. The mean PSQI global score was 8.6 (5.0) and 74.8% of patients were poor sleepers (PSQI total score ≥5). The mean ESS score was 8.8 (5.7). Approximately, 52% of all subjects were considered anxious (HADS-A, sub-score >7) and 43% were depressed (HADS-D, sub-score >7). The self-esteem component of IWQOL-Lite with the score of 26.0 (27.6 had the lowest score compared to the other components (Table 3-1).

In the present study, Pearson's correlation coefficients were used to assess the relationships between questionnaires scores, prior to conduct regression analysis. Pearson's correlation is a measure for the linear relationship between two continuous random variables. Pearson's correlation test is applicable for parametric data, thus it was used to assess the correlation between data from questionnaires in the present study. The correlation coefficient, r, ranges from -1 to +1, the closer r is to ±1 suggests the stronger the correlations. (Interpretation of value of r: 1.0 (i.e. perfect correlation), 0 to 1 (i.e. the two variables tend to increase or decrease together), 0.0 (i.e. the two variables do not vary together at all, -1 to 0 (i.e. one variable increases as the other decreases), -1.0 (i.e. perfect negative or inverse correlation)).

There was a statistically significant moderate negative correlation between PSQI score and IWQOL-Lite score (a correlation coefficient, $r = -0.26$, $p<0.01$). There was a statistically significant strong positive correlation between PSQI score and HADS-A score ($r = 0.30$, $p<0.01$). There was also a statistically significant moderate positive correlation between PSQI score and HADS-D score ($r = 0.25$, $p<0.01$). In addition,

there was a statistically strong negative correlation between ESS score and IWQOL-Lite ($r = -0.36$, $p<0.01$). There was a statistically significant weak positive correlation between ESS score and HADS-A score ($r = 0.22$, $p<0.01$). There was a statically significant moderate positive correlation between ESS score and HADS-D score ($r = 0.24$, $p<0.01$) (Table 3-2). The observed correlations between the variables of the present studies falls in the range of observed correlations from similar studies (Sandadi and colleagues,[328]Turkmen and colleagues,[321] Norra and colleagues[327]), which indicates that observed correlations in this study is typical for this area of research.

Table 3-1. Descriptive characteristics of 270 study participants.

Variable	*n* (%)	Mean (SD)
Age (years)		43.5 (12.4)
Females/Males	202 (74.8)/ 68 (25.2)	
BMI (kg/m^2)		46.9 (7.8)
Marital status		
Married	86 (51.4)	
Living with a partner	24 (14.4)	
Single	38 (22.8)	
Divorced	13 (7.8)	
Widowed	6 (3.6)	
Occupational status		
Unemployed	42 (23.0)	
Employed	113 (61.7)	
Retired	15 (8.2)	
Student	13 (7.1)	
Smoker	79 (29.3)	
Alcohol consumption	125 (46.3)	
Hypertension	91 (33.7)	
OSA	67 (24.8)	
Diabetes	71 (26.3)	
IWQOL-Lite		
Physical function		42.7 (25.6)
Self-esteem		26.0 (27.6)
Sexual life		42.5 (36.4)
Public distress		40.8 (29.1)
Work		51.9 (30.8)
Total score		42.0 (22.0)
HADS Anxiety		10.4 (4.5)
HADS Depression		9.1 (3.9)
PSQI global score		8.5 (5.1)
ESS total score		8.8 (5.7)

Body mass index (*BMI)*, obstructive sleep apnoea (*OSA)*, Impact of Weight on Quality of Life (*IWQOL-Lite)*, Hospital Anxiety and Depression Scale (*HADS)*, Pittsburgh Sleep Quality Index (*PSQI)*, Epworth Sleepiness Scale (*ESS).*

Table 3-2. Bivariate correlations between questionnaire scores.

	Age	BMI	ESS	IWQOL-Lite	HADS-A	HADS-D
BMI	0.02					
ESS	0.02	0.08				
IWQOL-Lite	0.04	-0.26**	-0.36**			
HADS-A	-0.18**	-0.02	0.22**	-0.51**		
HADS-D	-0.11	0.01	0.24**	-0.61**	0.65**	
PSQI	-0.06	0.03	0.24**	-0.26**	0.30**	0.25**

Body mass index (*BMI)*, Impact of Weight on Quality of Life (*IWQOL-Lite)*, Hospital Anxiety and Depression Scale (*HADS)*, Pittsburgh Sleep Quality Index (*PSQI),* Epworth Sleepiness Scale (*ESS).*

**Correlation is significant at the 0.01 level (2-tailed)

A series of multiple linear regression analyses was performed in order to evaluate the associations among levels of anxiety and depression symptoms with components and total score of PSQI and ESS; they are summarised in Table 3-3 and Table 3-4. Our analyses demonstrated that HADS-A and HADS-D scores (outcome variables) were significantly associated with all the components of PSQI except sleep disturbance, use of sleeping medication and daytime dysfunction ($p>0.05$). The PSQI global score had a positive significant association with anxiety ($\beta = 0.29$, $p = 0.01$) and depression ($\beta = 0.31$, $p \leq 0.01$) components of HADS (Table 3-3).

Table 3-3. Association between the Hospital Anxiety and Depression Scale (HADS) anxiety and depression scores with components and global score of the Pittsburgh Sleep Quality Index (PSQI).

	HADS-Anxiety (outcome)		**HADS-Depression (outcome)**	
(Predictors)	**β (SE)**	**P** [a]	**β (SE)**	**P** [a]
Sleep quality	0.35 (0.44)	**0.001**	0.30 (0.46)	**0.009**
Sleep latency	0.29 (0.46)	**0.019**	0.26 (0.46)	**0.041**
Sleep duration	0.24 (0.41)	**0.037**	0.26 (0.40)	**0.028**
Habitual sleep efficiency	0.32 (0.39)	**0.006**	0.43 (0.37)	**0.000**
Sleep disturbance	0.11 (0.16)	0.335	0.04 (0.15)	0.707
Use of sleeping medication	0.09 (0.45)	0.452	0.04 (0.45)	0.705
Daytime dysfunction	0.08 (0.50)	0.452	0.18 (0.49)	0.136
Global PSQI score	0.29 (0.07)	**0.010**	0.31 (0.07)	**0.009**

[a] Adjusted for age, gender, hypertension, diabetes and Obstructive Sleep Apnoea (*OSA*).

The HADS-Anxiety was associated with all the components of ESS except the score of dozing off in the situation "car in traffic" ($p>0.05$). This question is commonly answered in the negative by patients because of concerns about driving licences. The HADS-D was associated with all the components of ESS except the score of dozing off in the situations of; "sitting and reading" and "car in traffic" ($p>0.05$). The excessive daytime sleepiness is highly associated with anxiety ($\beta = 0.44$, $p<0.001$) and depression ($\beta = 0.41$, $p = 0.01$) components of HADS (Table 3-4).

Table 3-4. Association between the Hospital Anxiety and Depression Scale (HADS) anxiety and depression scores with components and total score of the Epworth Sleepiness Scale (ESS).

	HADS-Anxiety (outcome)		**HADS-Depression (outcome)**	
(Predictors)	**β (SE)**	**P** [a]	**β (SE)**	**P** [a]
Sitting and reading	0.31 (0.41)	**0.005**	0.16 (0.41)	0.193
Watching TV	0.36 (0.45)	**0.002**	0.34 (0.45)	**0.006**
Inactive in public	0.36 (0.48)	**0.001**	0.28 (0.48)	**0.019**
Car passenger	0.38 (0.36)	**0.001**	0.44 (0.35)	**0.000**
Lying down	0.31 (0.44)	**0.007**	0.38 (0.42)	**0.002**
Sitting talking	0.33 (0.75)	**0.004**	0.45 (0.69)	**0.000**
Sitting quietly	0.32 (0.43)	**0.005**	0.29 (0.44)	**0.016**
Car in traffic	0.22 (0.64)	0.060	0.14 (0.63)	**0.256**
ESS total score	0.44 (0.08)	**0.000**	0.41 (0.07)	**0.001**

[a] Adjusted for age, gender, hypertension, diabetes and Obstructive Sleep Apnoea (*OSA*).

The association of IWQOL-Lite (outcome variable) with PSQI global score and ESS total score are presented in Table 3-5. After adjusting for age, gender, hypertension, diabetes and OSA, PSQI was significantly associated with physical function (β = -0.32, $p<0.01$), self-esteem (β = -0.23, $p = 0.03$), sexual-life (β = -0.30, $p = 0.01$), public distress (β = - 0.39, $p<0.01$), work (β = -0.26, $p = 0.02$), and total score (β = -0.35, $p<0.01$). Similarly, ESS were also associated with physical function (β = -0.27, $p<0.01$), self-esteem (β = -0.30, $p<0.01$), sexual-life (β = -0.35, $p<0.01$), public distress (β = -0.39, $p = 0.001$), work (β = -0.48, $p<0.001$), and total score (β = -0.42, $p<0.001$).

Table 3-5. The association between subjective sleep disturbances (PSQI global score and excessive daytime sleepiness) with components of the IWQOL-Lite (Impact of Weight on Quality of Life).

Variable	β	t	R^2	F	*P* [a]
Outcome: Physical function					
Predictor: *Pittsburgh quality of life index*	-0.32	-3.13	0.30	5.39	**0.002**
Predictor: *Epworth sleepiness scale*	-0.27	-2.62	0.30	5.01	**0.011**
Outcome: Self-esteem					
Predictor: *Pittsburgh quality of life index*	-0.23	-2.21	0.23	3.82	**0.030**
Predictor: *Epworth sleepiness scale*	-0.30	-2.71	0.22	3.28	**0.009**
Outcome: Sexual life					
Predictor: *Pittsburgh quality of life index*	-0.30	-2.49	0.13	1.67	**0.015**
Predictor: *Epworth sleepiness scale*	-0.35	-2.91	0.17	2.08	**0.005**
Outcome: Public distress					
Predictor: *Pittsburgh quality of life index*	-0.39	-3.45	0.15	2.92	**0.001**
Predictor: *Epworth sleepiness scale*	-0.39	-3.50	0.17	2.31	**0.001**
Outcome: Work					
Predictor: *Pittsburgh quality of life index*	-0.26	-2.27	0.15	1.78	**0.026**
Predictor: *Epworth sleepiness scale*	-0.48	-4.56	0.31	4.94	**0.000**
Outcome: Total score					
Predictor: *Pittsburgh quality of life index*	-0.35	-3.16	0.17	2.72	**0.002**
Predictor: *Epworth sleepiness scale*	-0.42	-3.94	0.26	4.01	**0.000**

[a] Adjusted for age, gender, hypertension, diabetes and Obstructive Sleep Apnoea (*OSA*).

Note: t; t-statistic is the regression coefficient of the independent variable divided by its standard error. A t-stat larger than +2 or less than -2 indicates that independent variable has a significant impact on dependant variable (having greater confidence in the coefficient as a predictor). R^2; a statistical measure of how close the data are to the fitted regression line with values range from 0.0 to 1.0. Higher values indicate that the model fits the data better. F; a value that determines if the variance between two populations are significantly different and this value determines the p-value. If the null hypothesis is true, it is expected F to have a value close to 1.0 most of the time. A large F ratio means that the variation among group means is meaningful and not happened by chance.

I tested an SEM (Figure 3-3), representing the hypothesised model in which the *Poor Sleep Factors* latent was defined by two variables; ESS and PSQI, and the *Obesity-Related Conditions* latent was defined by three variables; hypertension, diabetes and OSA; was set to predict the total IWQOL-Lite score and HADS-Depression score (endogenous variables). The result postulated that our hypothesised model has a good fit to the data. The CFI was 0.988, the GFI was 0.953, the AGFI was 0.881, the SRMR was 0.056, and the RMSEA was 0.034, with a 90% confidence interval of 0.000–0.135 indicating a good fit of the model. Obesity-Related Conditions was negatively associated with HADS-D (β = -0.16; $p<0.05$), Poor Sleep Factors was positively associated with HADS-D (β = 0.82; $p<0.001$) and was negatively associated with IWQOL-Lite (β = -0.79; $p<0.001$). A summary of standard errors, direct effects, indirect effects and total effects based on 1000 bootstrap sample is presented in Table 3-6. The strongest standardized total (direct and indirect) effect was of Poor Sleep Factors on HADS-D and was 0.82.

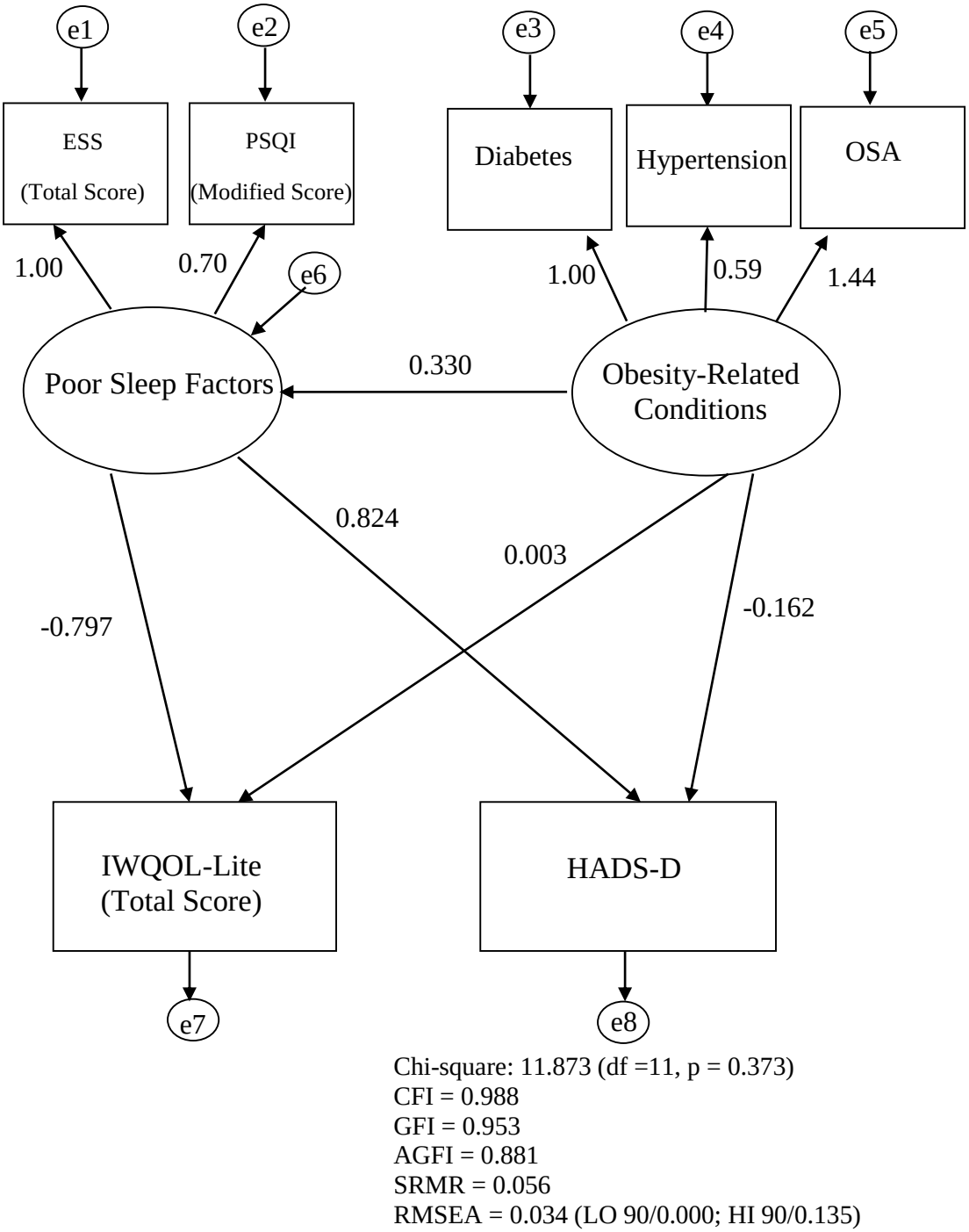

Figure 3-3. Measurement (standardised estimates) of hypothesised structure equation model (SEM). Pittsburgh Sleep Quality Index (*PSQI*), Epworth Sleepiness Scale (*ESS*), Obstructive Sleep Apnoea (*OSA*), Impact of Weight on Quality of Life-Lite (*IWQOL-Lite*), Hospital Anxiety and Depression Scale-Depression (*HADS-D*), Comparative Fit Index (*CFI*), Goodness-of-fit statistic (*GFI*), Adjusted Goodness-of-Fit statistic (*AGFI*), Standardised Root Mean Square Residual (*SRMR*), Root Mean Square Error of Approximation (*RMSEA*).

Table 3-6. Standardised effect sizes based on 1000 bootstrap samples

Predictor	Response	Standard error	Direct effect	Indirect effect	Total effect
Obesity-related conditions	Poor sleep factors	2.812	0.330		0.330
Obesity-related conditions	HADS-D	2.880	-0.434	0.272	-0.162*
Obesity-related conditions	IWQOL-Lite	14.377	0.266	-0.263	0.003
Poor sleep factors	HADS-D	0.255	0.824		0.824**
Poor sleep factors	IWQOL-Lite	1.346	-0.797		-0.797**

Hospital Anxiety and Depression Scale-Depression (*HADS-D*), Impact of Weight on Quality of Life-Lite (*IWQOL-Lite*).
* p <0.05
** p <0.001

3.6 Discussion

The present study found that poor sleep quality (measured using PSQI) mean (SD) 8.5 (5.1), anxiety symptoms (measured using HADS-Anxiety) 10.4 (4.5), depression symptoms (measured using HADS-Depression) 9.1 (3.9), and reduced quality of life (measured using IWQOL-Lite) 42.0 (22.0) were highly prevalent among patients with extreme obesity. More than two thirds of patients with extreme obesity reported poor sleep quality and the average self-reported sleep duration was 6.2 (1.5) hours. I also found that sleep quality correlated significantly with anxiety (β (SE) (0.29 (0.07), p = 0.01) and depression (β (SE) (0.31 (0.07), p = 0.009), with the observed associations were stronger for depression than for anxiety. Sleep quality were also significantly correlated with quality of life (β -0.35, p = 0.002). Moreover, daytime sleepiness correlated significantly with anxiety (β (SE) (0.44 (0.08), p<0.001) and depression (β (SE) (0.41 (0.07), p = 0.001) and also with quality of life (β -0.42, p<0.001). The associations above were controlled for age, gender, hypertension, diabetes, and OSA, indicating these associations are independent of these potential confounders, particularly OSA.[337]

3.6.1 Sleep patterns in extreme obese population

The results of the present study demonstrate that extremely obese individuals have a short average sleep duration (mean sleep = 6.2 hours) and reported poor sleep quality (mean PSQI= 8.6). This is in agreement with recent observation by Toor and colleagues[338] who evaluated the sleep duration of 45 bariatric patients with extreme obesity (mean body mass index = 49 kg/m^2) compared to 45 non-obese controls. The study also reported that obese individuals slept less (6 hours per night) compared to control group reported sleeping 7 hours per night. Obese individuals also had a higher

PSQI score (8.5) than their non-obese controls (4.5). It was reported that bariatric surgery dramatically improved both sleep duration and quality. Similarly, in a large epidemiological study[339] involving 2,803 adult participants from China, obese individuals (n = 617) had a higher PSQI global score (7.02 ± 2.95) compared to overweight (n = 1,127, 6.61 ± 2.96) and normal weight (n = 1,059, 6.30 ± 2.56). Moreover, other factors in addition to obesity including duration of sleep, and female gender were found to be significantly associated with poor sleep quality even after controlling for potential confounders such as cardiometabolic risk factors.[339] Interestingly, obese individuals with poor sleep may be less likely to be successful in weight loss programmes. In a randomised controlled study, Thomson and colleagues[340] assessed whether female participants (mean age 45.5 years, mean BMI 33.9 kg/m^2) with a better PSQI global score or sleep duration of >7 hours per night would achieve greater weight loss compared to those with a lower PSQI score or sleep duration of ≤7 hours per night over the 6 month study duration. Findings indicated that a better PSQI score was associated with 33% higher chance for weight-loss success (weight loss success: achieving >5% weight loss compared to baseline) (Relative risk (RR) 0.67, 95% CI, 0.52 - 0.86).

Extreme obese individuals in this study had a short sleep duration and poor sleep quality as assessed by the PSQI. Cumulative evidence from epidemiological and experimental studies suggests that both short sleep duration and poor sleep quality are associated with a higher risk for obesity as well as several other adverse health outcomes such as hypertension, diabetes, and cardiovascular complications among individuals with different age, ethnicity, and socioeconomic background.[113, 114] The consequences of poor sleep have not been previously studied among individuals with

extreme obesity. There is a need for future studies to assess the impact of short or poor sleep among extreme obese population.

Based on findings of present study and also the highlighted evidence, it is known that individuals with obesity are more likely to suffer from poor sleep. It can be argued that obesity per se may be the main cause for sleep disruption. Obese individuals normally suffer from several obesity-related conditions such as difficulty breathing, urinary incontinence, body temperature dysregulation, and pain, which may contribute to poor sleep quality. Additionally, it was hypothesised that mental health problems may be a potential mediator on the causal pathway between poor sleep and obesity. Recently, Bidulescu and colleagues[158] analysed data from 1,515 residents of metropolitan Atlanta, aged 30-65 years with mean BMI of 29.4 kg/m^2 in the Cardiovascular Health Epidemiology Study (CHES), and found that poor sleep quality was associated with increased risk for obesity (OR 1.08, 95% CI 1.03 – 1.12), but after adjustment for stress the association was diminished, suggesting that perceived stress mediated the associations between reduced sleep quality and obesity.

3.6.2 Symptoms of depression in extreme obese population

The extreme obese individuals in the study also reported a high level of anxiety (mean HADS-Anxiety score 10.4) and depression (mean HADS-Depression score 9.1). Similar studies also in line with this finding consistently suggest that depressive symptoms are prevalent among obese individuals.[341] Epidemiological evidence suggests that there is a positive association between obesity and depressive symptoms. For example, Simon and colleagues[342] collected data using telephone interviews from 4,641 women aged 40 to 65 years old. They found that those with a BMI of 35 kg/m^2 or more were 4 times more likely to report depressive symptoms compared to those

with a BMI of less than 25 kg/m^2 (OR 4.95, 95% CI 3.47 – 7.05), and such associations were remained significant even after multivariate adjustment for factors including: age, race, marital status, education level, smoking status, and using of anti-depressant medications. In another study, Zhao and colleagues[343] analysed data from a cross-sectional, nationally representative sample of 2,439 U.S. adults (1,325 men and 1,114 women) who were aged 20 years and above and found that individuals with abdominal obesity, defined as waist circumference of >102 cm for men and >88 cm for women were more likely to have major (OR 2.18, 95% CI 1.35 – 3.59) or moderate (OR 2.56, 95% CI 1.34 – 4.90) depressive symptoms compared to those without abdominal obesity. Similarly, Dunbar and colleagues[344] analysed data from a representative sample of 1,690 Australian, aged 25 to 84 years. They reported that waist circumference was significantly associated with higher risk of higher HADS score among these individuals (OR 2.86, 95% CI 2.66 – 3.06).

Based on results from current study and studies discussed earlier, depression is prevalent among individuals with obesity. The current study is unique in investigating the extreme obese population. Depression among extreme obese individuals may worsen obesity per se. Increased food intake and appetite are believed to be associated with depression.[341] It is also believed that depression is associated with increased weight gain through excessive alcohol consumption.[341]On the other hand, depressed obese individuals are less likely to have a desire to take part in weight loss programmes. However, evidence indicates that weight loss may potentially reduce depressive symptoms.[286] It is important that depressive symptoms among obese individuals should be addressed and treated to prevent further deleterious consequences of depression among these individuals.

The underlying mechanism for the association between obesity and depression is yet to be understood. Obesity is associated with stigma and obese individuals, particularly women are less likely feel like appearing in public places and they may also suffer from lower self-esteem that has been linked to depression.[345] Obesity, can be accompanied by pain as result of multiple co-morbidities, which can cause limitations in physical movement, which can ultimately lead to depression though reduced involvement in pleasurable activities.[346]

3.6.3 Impaired quality of life among extreme obese population

The results of the current study showed that extreme obese individuals reported lower score in all five components of the IWQOL-Lite (physical function = 42.7, self-esteem = 26.0, sexual life = 40.8, work = 51.9). Current evidence also indicates that impaired quality of life is prevalent among obese individuals. In line with my finding, Fontaine and colleagues[347] evaluated HRQoL measured by the Study Short Form-36 Health Survey (SF-36) among 312 adult individuals seeking outpatient obesity treatment and they found that individuals with extreme obesity (mean body mass index = 48.7 kg/m^2) were more likely to report impairment on all eight quality-of-life domains and in particular on the physical and social components. Recently, McDonough and colleagues[348]analysed data from 4,989 adult men and women and found that compared to normal weight individuals (n = 1,230), overweight (n = 2,154, OR 1.22, 95% CI 1.10 - 1.41) and obese (n = 1,605, OR 1.81, 95% CI 1.56 - 2.10) individuals were more likely to report lower health-related quality of life (HRQoL) scores. Results from similar studies showed that in general obese individuals tend to report discrete reductions in all aspects of the HRQoL, with a dose-response relationship between

BMI and impaired HRQoL. Finally the majority of obese individuals reported higher impairment in physical function as a result of pain.[349]

Studies that evaluated HRQoL among the obese population utilised generic measures such as SF-36, or more obesity-specific measures such as IWQOL-Lite. Each measure provides data on different domains of quality of life, therefore it is very difficult to compare such results and draw a confirmative conclusion on how obesity may affect HRQoL. IWQOL-Lite is a new instrument that has been designed to assess the effect of weight on a number of life components.[350] However, validation studies for IWQOL-Lite are largely lacking. Overall, assessment of HRQoL may provide a better understanding of the psychosocial impact of excess body weight not only for clinicians and obesity researchers, but also for obese individuals. As weight gain occurs gradually over time, the majority of obese individuals may not be aware of the adverse consequences of their weight on important quality of life dimensions such as social functioning. Based on my results, extreme obese individuals obtained the lowest score on the self-esteem domain (26.0), and such assessment may help people with obesity to identify their significant milestones and help them focus more on their effort toward achieving their goals for weight control. Assessment of HRQoL of individuals with obesity can also help designing future treatment interventions to address unique individual needs.

It is not known how obesity may affect HRQoL. It is believed that there is a high level of stigmatisation and discrimination attached to obesity, which could potentially affect all aspects of an obese individual's life.[341] In a longitudinal study by Gortmaker and colleagues[351] 10,000 individuals aged 16 to 24 years at baseline, were followed for 7 years and the consequences of weight gain on socioeconomic life of these people was

assessed. Overweight individuals were less likely to have a higher education (0.3 year less; 95% CI 0.1 - 0.6) and lower income levels ($6,710 less per year; 95% CI $3,942 - $9,478) and also were less likely to get married (20% less likely; 95% CI 13% - 27%).[351] In another study[352] with 57 severely obese, 91% of the obese individuals reported that they perceived discrimination at work and also in public places, and within their families. Furthermore, 84% declared they avoided public appearances.[352] Evidence also indicates that weight loss, via bariatric surgery may induce dramatic improvements on all aspects of HRQoL.[349] Extreme obese individuals that underwent weight loss surgery obtained better scores on mobility, sexual activity, self-esteem, and social interaction.[349] Moreover, a longer follow-up of the patients (over 1-year period) showed that such improvements on HRQoL are durable.[349]

3.6.4 Associations among sleep quality, depression and quality of life among extreme obese individuals

The result of the present study showed that poor sleep quality and excessive daytime sleepiness were strongly associated with mood disturbance and poorer quality of life. Such associations remained significant even after controlling for age, gender, hypertension, diabetes, and obstructive sleep apnoea (OSA). To my knowledge, this is the first study that investigated such associations among the extreme obese population, with other studies evaluated association between poor sleep and depressive symptoms and quality of life among non-obese participants with various morbidities. For example, recently, Turkmen and colleagues[321] studied 63 haemodialysis older (aged 65 to 89 years) non-obese patients (32 women; mean BMI 23.9 kg/m^2) and found that poor sleepers were more likely to report depressive symptoms and impaired HRQoL compared to good sleepers. Poor sleep quality found to negatively correlated with physical ($r = -0.50$, $p<0.001$) and mental ($r = -0.53$, $p<0.001$) components of HRQoL

and positively ($r = 0.60$, $p<0.001$) correlated with depression. In another study, Norra and colleagues[323] reported that poor sleep quality was significantly associated with depressive symptoms ($R^2 = 0.40$) among 204 patients with heart disease (mean age= 41.6 years). Similarly, Sandadi and colleagues[328] studied 86 women with a mean age of 58.1 years that had been diagnosed with ovarian cancer, and they found that the PSQI score was significantly and inversely correlated with all aspects of QoL (physical component $r = -0.59$, $p<0.001$, functional component $r = -0.69$, $p<0.001$, social component $r = -0.21$, $p<0.001$, emotional component: $r = -0.37$, $p<0.001$, fatigue component; $r = -0.65$ $p<0.001$) and were positively correlated with depression ($r = 0.53$, $p<0.001$).

I investigated whether PSQI and ESS scores are predictors of higher HADS-A, HADS-D scores, and IWQOL-Lite via the utilisation of linear regression models. Since the data were cross-sectional, causal pathways among these variables cannot be inferred. I used SEM analysis to test whether poor sleep factors negatively influence mood or vice versa. Interestingly, the model that was presented earlier supported our prior findings. I hypothesised that sleep can be influenced by obesity-related conditions, and both poor sleep factors and obesity-related conditions may influence quality of life and mood of the participants. In an on-going randomised controlled study, Cizza and colleagues[353] testing the hypothesis on whether increasing total sleep duration in sleep-deprived obese participants would have an impact on their body weight. The study randomised 150 obese patients, aged 35 years and older who reported sleeping less than 6 hours per night to the extension sleep intervention and control groups. Data on the endocrine and immune function of these individuals in both groups will be collected and compared. The results of this study and potential future studies may draw a new horizon on tacking obesity.

The mechanism underlying the association between sleep disturbance and reduced quality of life is not known. The sleep disturbances and particularly daytime sleepiness can result in low energy levels, which could be a potential marker for impaired physical function of HRQoL. Additionally, the association between sleep and depression is complex and the bi-directional association between sleep and depression makes it difficult to infer any causal pathways between them.[354] It is believed that obese individuals with sleep problems may be frustrated with battling for a better night's sleep and develop depression over time.

3.6.5 Clinical implications

Results of the present study are statistically significant showing strong associations between the questionnaire score. The effects are very small and are unlikely to be clinically significant. The findings, however, cannot estimate the impact of improvements in sleep on quality of life and depression and anxiety. Future longitudinal/intervention studies with objective measures of sleep are needed to measure the change in scores of questionnaires measuring health-related quality of life and anxiety/depression, in order to establish clinically meaningful change scores of such questionnaires among people with extreme obesity.

The study's findings have clinical implications. The results of the present study highlighted that extremely obese individuals had a short average sleep duration (mean sleep = 6.2 hours) and reported poor sleep quality (mean PSQI = 8.6). As it was discussed earlier in this chapter, poor sleep quality has other adverse outcomes such as failure to achieve weight loss among obese patients, thus sleep problems should be detected and addressed among these individuals. The impact of sleep disorders on various aspects of individuals' lives should not be underestimated. It is very important

to design mechanisms to screen for sleep problems among obese individuals. Routinely screening for sleep disorders by being aware of clinical symptoms can help clinicians more accurately diagnose such disorders. Because time is an important factor in clinical practice, barriers might exist in implementing such routine screening programmes. Nonetheless, starting to screen for sleep problems, can be as simple as asking the patient if they snore, if they feel tired during the day, if they have difficulties initiating sleep/maintaining asleep, or if they have noticed any changes in their mood. Healthcare providers can also administer sleep scales tools such as Epworth Sleepiness Scale (ESS), Pittsburgh Sleep Quality Index (PSQI), and Berlin questionnaire. If the patient's responses to a screening tool indicate a sleep problem, it would be appropriate to refer them to sleep specialist for further evaluation. The sleep specialists can aid in diagnosing and managing sleep disorders. Future intervention studies are needed to explore the effects sleep disorders treatment on depressive symptoms and quality of life among people with extreme obesity.

The prevalence of sleep problems such as excessive daytime sleepiness and short sleep duration is relatively high among these obese subjects.[168] Although short sleep duration has been recognised as an important risk factor for obesity, data on the effect of sleep treatment and on obesity are unavailable. The treatment of sleep could potentially prevent worsening obesity and could also prevent the initiation and progression of psychological conditions such as depression among these individuals. In a randomised controlled trial, Reid and colleagues[355] investigated the effectiveness of aerobic exercise and sleep hygiene education programme on sleep, mood, and quality of life adults aged 55 years and older. Their results showed that compared to control group, the physical activity group had a significant reductions on PSQI global scores ($p<0.001$) and several sub-scores; sleep latency ($p = 0.04$), sleep duration ($p =$

0.04), daytime dysfunction (p = 0.02), and sleep efficiency (p = 0.03). Moreover, individuals in the physical group also had improvements in depressive symptoms (p = 0.04), daytime sleepiness (p = 0.02) compared to controls.[355]

3.6.6 Strengths and limitations

To date, no studies have previously investigated the associations between poor sleep factors and depression and anxiety symptoms of extreme obese population. The study has the merit of detailed statistical analysis. I used SEM analysis to test whether poor sleep factors negatively influence mood or vice versa. It is of interest that the model that was presented earlier supported the prior findings. The result demonstrated that poor sleep factors are strongly associated with higher levels of depression and also inversely associated with quality of life. The hypothesised model had a strong evidence (p-value>0.05) indicating that the hypothesised model fitted the data. Other hypotheses for the model were also tested such as if the mood and quality of life would predict sleep disturbances, but the p-value for the model fit was not good. Similar studies found that there is a strong bi-directional association between sleep disturbance with mood and also sleep disturbance with quality of life. Future longitudinal studies using objective measurements are needed to investigate the causal pathway in depth and also investigate the underlying mechanisms.

The main limitation of the study is its cross-sectional design, so a direct causal relationship between sleep disturbances and anxiety and depressive symptoms cannot be inferred. The other limit is using self-report questionnaires. However, PSQI is a reliable and validated instrument, although it cannot be used as an accurate diagnostic tool.

3.6.7 Key points

The participants reported shorter sleep duration and low sleep quality scores. I found that depression and anxiety scores were high among extreme obese individuals. The participants reported lower scores across all components of the IWQOL-Lite (quality of life), and especially the self-esteem component. The PSQI global and ESS scores were associated with anxiety and depression symptoms. The PSQI global and ESS scores were associated with poor quality of life. The SEM model supported the direction of the associations that were previously inferred from the linear regression models. Routine screening for sleep disorders in obese populations could be beneficial, as the early detection of such problems could prevent the potential development and perpetuation of psychological disorders among these individuals that may impact on their efforts to address their obesity.

4 EFFECTIVENESS OF LIFESTYLE INTERVENTIONS ON OBSTRUCTIVE SLEEP APNOEA (OSA): SYSTEMATIC REVIEW AND META-ANALYSIS

4.1 Abstract

Introduction: Obstructive sleep apnoea (OSA) is a common sleep disorder associated with several adverse health outcomes. Given the close association between OSA and obesity, lifestyle and dietary interventions are commonly recommended to patients. However, the evidence for their impact on OSA has not been systematically examined. The main objective of this study was to conduct a systematic review and meta-analysis to assess the impact of weight loss through diet and physical activity on measures of OSA: apnoea–hypopnoea index (AHI) and oxygen desaturation index (ODI).

Methods: A systematic search was performed to identify publications using MEDLINE (1948-2011 week 40), EMBASE (from 1988-2011 week 40), and CINAHL (from 1982-2011 week 40). An inverse variance method was used to weight studies and the random effects model was used to analyse data.

Results: Seven randomised controlled trials (519 participants) showed that weight reduction programmes were associated with a decrease in AHI (-6.04 events/hour [95% confidence interval -11.18 to -0.90]) with substantial heterogeneity between studies (I^2 = 86%). Nine uncontrolled before-after studies (250 participants) showed a significant decrease in AHI (-12.26 events/hour [95% confidence interval -18.51, -6.02]). Four uncontrolled before-after studies (97 participants) with ODI as outcome also showed a significant decrease in ODI (-18.91 episodes/hour [95% confidence interval -23.40 to -14.43]).

Conclusion: Published evidence suggests that weight loss through lifestyle and dietary interventions results in improvements in OSA parameters, but is insufficient to normalise them. The changes in OSA parameters could, however, may be clinically relevant in some patients by reducing OSA severity. These promising preliminary results need confirmation through larger randomised studies including more intensive weight loss approaches.

4.2 Introduction

4.2.1 Epidemiology of obstructive sleep apnoea

4.2.1.1 Description of condition

Obstructive sleep apnoea (OSA) is a common sleep disorder, which is characterised by complete or partial collapse of upper airway. OSA is associated with episodic hypoxia, arousal, and sleep fragmentation.[105] OSA commonly presents with excessive daytime sleepiness. Other reported symptoms include nocturia, gastro-oesophageakl reflux disease, early morning headaches, sexual dysfunction, and reduced quality of life.[356] According to the American Academy of Sleep Medicine (AASM) guideline, a complete collapse of the airway is defined as an apnoea and partial airway collapse is defined as an hypopnoea (Table 4-1).[357]

Table 4-1. Definition of apnoea and hypopnoea according to the American Academy of Sleep Medicine (AASM) guideline.[357]

Term	Definition
Apnoea (Figure 4-1)	• Drop in airflow by >90% of pre-event baseline • Duration >10 seconds
Hypopnoea (Figure 4-2)	• Drop in airflow by >30% from pre-event baseline • Duration >10 seconds • 3% oxygen desaturation or associated with an arousal

Overnight polysomnography (PSG) is the gold standard diagnostic tool for OSA,[105] and provides the apnoea-hypopnoea index (AHI) which is a common measure that is widely used to assess presence and severity of OSA. AHI is calculated using the following equation:

$$\text{AHI} = \frac{\text{Total number of apnoea events} + \text{Total number of hypopnoea events}}{\text{Total number of minutes of acutual sleep time}} * 60$$

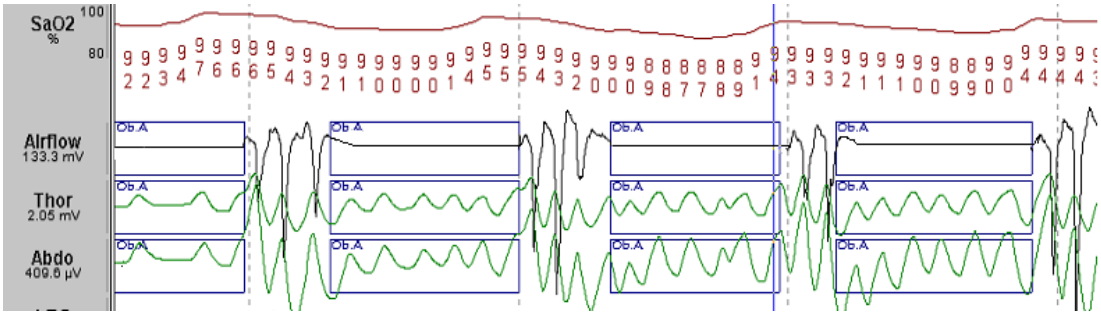

Figure 4-1. Apnoeas: drops in airflow by >90% of pre-event baseline lasting >10 seconds. Note that apnoeas in this recording are accompanied by oxygen desaturation (SaO2%). There is thoracic and abdominal effort, but no airflow. The presence of effort distinguishes an obstructive apnoea from a central apnoea where there is no airflow and no effort.

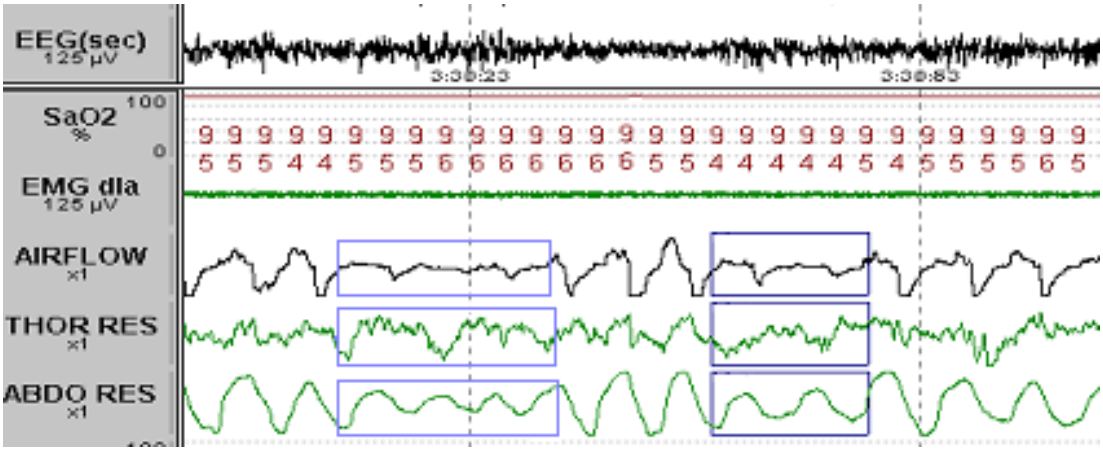

Figure 4-2. Hypopnoeas: drops in airflow by >30% of pre-event baseline, lasting >10 seconds and associated with oxygen desaturation or arousal. There is thoracic and abdominal effort, but airflow is reduced. The first event highlighted is associated with an arousal.

OSA is defined as AHI ≥5 events/hour of sleep. Based on different thresholds of AHI, OSA is categorised into three groups: mild OSA (AHI 5-14 (events/hour)), moderate OSA (AHI 15-30 (events/hour)) and severe OSA (AHI ≥30 (events/hour)).[357] Similar to AHI, there are other indices (Table 4-2) that are also used in the clinical setting such as respiratory disturbance index (RDI) and oxygen desaturation index (ODI).[105]

Table 4-2. Different indices to measure severity of OSA.

Term	Definition
Apnoea-Hypopnoea Index (AHI)	The total number of complete obstructions of upper airways (apnoea) and partial obstructions (hypopnoea) per hour of sleep
Respiratory Disturbance Index (RDI)	The combined number of apnoeic and hypopnoeic episodes per hour of sleep
Oxygen Desaturation Index (ODI)	A drop in blood's oxygen level by 4 per cent per hour of sleep

4.2.1.2 Prevalence of OSA

Cumulative evidence from Western countries indicates that the prevalence of sleep apnoea for adults is 3 to 7% among males and 2 to 5% among females.[105, 358-360] In 1993, in the US, Young and colleagues[360] assessed the frequency of episodes of apnoea and hypopnoea per hour of sleep among 602 men and women 30 to 60 years old via overnight PSG. Their results demonstrated that the apnoea-hypopnoea score of 5 or greater was present in 4% of men and 2% of women. It was also postulated that obesity was significantly associated with OSA and severe cases of the disease was substantially more prevalent among habitual snorers. Similar large population-based studies have been conducted in United States,[360, 361] Spain,[362] India,[363] China,[364, 365] Korea,[366] and, Australia.[367] (Table 4-3)

Determining the precise prevalence of OSA is controversial, as diversity in sampling methods, differences in diagnostic test employed, and variability in defining the disease may lead to differences in the prevalence of OSA. It is estimated that the prevalence of OSA may vary across different population subsets and it may be higher among overweight/obese, African-American, older people (≥65 years old), and also among individuals with craniofacial abnormalities.[360, 361]

Table 4-3. Summary of studies investigated the prevalence of obstructive sleep apnoea.

Authors and year	Country	Sample size	Diagnostic measure	Prevalence	
				Male	Female
Young et al,[360] 1993	United States	602	PSG	4%	2%
Bixler et al,[361] 2001		1,741	PSG	3.9%	1.2%
Marin et al,[362] 1997	Spain	1,360	NHO	2.2%	0.7%
Udwadia et al,[363] 2004	India	250	PSG	7.5%	4.5%
Ip et al,[365] 2001	China	258	PSG	4.1%	-
Ip et al,[364] 2004			PSG	-	2.1%
Kim et al,[366] 2004	Korea	457	PSG	4.5%	2.2%
Bearpark et al,[367] 1995	Australia	485	MESAM IV[a]	3.1%	-

Polysomnography (*PSG)*, nocturnal home oximetry (*NHO*)

[a] MESAM: device that measures oxygen saturation, heart rate, snoring, and body position

4.2.1.3 Pathophysiology of OSA

The pathophysiology of OSA is complex. In normal condition during both sleep and wakefulness, the net acting forces tend to keep the upper airways patent. However it is not the case in apnoeic individuals.[360] It is believed that anatomic factors may

increase the susceptibility of airways to collapse during inspiration or insufficient neuromuscular compensation predispose upper airway to be obstrcuted.[368] It has been hypothesised that factors such as age, gender, and ethnicity may affect the contribution of anatomic versus neuromuscular factors in occurrence of OSA. However epidemiological data are extensively lacking to support such hypothesis. In contrast to OSA, central sleep apnoea may lead to a decrease in neural output of respiratory motoneurons in the absence of airways obstruction.[368] In general, there may be an overlap in the pathophysiology of these two conditions. However, the anatomic factors play an important role in pathogenesis of OSA. The functionality of oropharyngeal and abductor muscles may be diminished as a result of decreased neural output and it may either lead to central apnoea if upper airways are anatomically less prone to collapse or may lead to OSA if upper airways are anatomically more prone to collapse.[369] Despite the important role of anatomic abnormalities in the pathogenesis of OSA, it has been suggested recently that sleep apnoea may be a manifestation of metabolic abnormalities.[370] There is a close link between OSA and factors associated with metabolic syndrome such as obesity, male gender, post-menopausal state, hypertension and diabetes.[370] As OSA is featured by various factors including: weight gain, snoring, respiratory cessation, somnolence, further weight gain and severe breathing abnormalities, all suggesting that it is a systematic condition and cannot solely be the result of a local abnormality in respiratory system.[161] There is an on-going debate whether OSA should be considered an anatomic disorder or a manifestation of metabolic syndrome.

The evidence from Wisconsin Sleep Cohort Study (WSCS) indicates that body weight alteration can predict the severity OSA. For instance, 10% weight gain compared to baseline was associated with an increased risk for progression of moderate to severe

OSA up to 6-fold (95% CI, 2.2 – 17.0). On the other hand, a 10% weight reduction was associated with a 26% reduction in AHI (95% CI, 18% -34%).[161] Similarly, findings over a 5-year period from the Sleep Heart Health Study[371] demonstrated that 10 kg weight gain was a strong predictor of a higher RDI (15 events per hour ≥) in men (OR 5.21, 95% CI 2.35 – 11.53), but such a trend was not clinically significant among women. The influence of body weight on the development of OSA was also observed in the Cleveland Family Study,[372] which postulated that age (per 10-year increase, OR 1.79; 95% CI, 1.41 – 2.27), gender (men vs. women OR 4.12, 95% CI 2.29 – 7.43) and body mass index (per 1 unit increase OR 1.14, 95% CI 1.10 – 1.19) have a very important role in the incidence and progression of sleep apnoea over time.

The longitudinal change in body weight and its impact on AHI suggests that overweight/obese individuals are at greater risk of developing the disease. With the enormous rise in prevalence of obesity across different countries, it is not surprising to observe an increase in the prevalence of OSA, which could potentially impose an additional burden on healthcare resources.

4.2.1.4 Risk factors of OSA

Understanding risk factors for OSA could be beneficial in terms of detecting the individuals who are at increased risk for developing the condition and directing sufficient diagnostic attention to them to prevent the development of further adverse consequences of the condition. Some of main the risk factors for OSA including, age, gender, ethnicity, overweight/obesity, genetics, craniofacial anatomy, smoking and alcohol consumption are discussed below.

4.2.1.4.1 Age

According to several epidemiological studies,[361, 373] the prevalence of moderate OSA (AHI ≥ 15 events/hour) varies widely between 7 to 44% in aged population, and differences in the prevalence diminish significantly after the menopause. Interestingly, the increase in the prevalence of OSA plateaus around age 65 years. However, the underlying mechanisms are unclear; there are several hypotheses to explain the phenomenon. It is believed that the effect of BMI on AHI is less strong among older individuals compared to middle-aged individuals.[361, 374]Other explanation includes lack of a bedtime partner to report sings such as snoring and apnoeas.

In general, the occurrence and implication of OSA in older adults compared to younger and middle-aged adults is under debate. It has been previously reported that OSA was weakly correlated with common risk factors such as excessive weight and common symptoms such as snoring among older individuals.[374] The impact of OSA is also different between younger and older individuals. OSA is associated with increased impairment in cognitive function in older adults, whereas it is associated with increased cardiovascular complications in younger individuals.[360]

There are some underlying factors that explain the link between ageing and OSA. Advancing age has been found to be an independent risk factor for functional impairment of pharyngeal dilator muscles, which lose their ability to maintain patentcy.[374] Older individuals are more susceptible to OSA as ageing is associated with changes in the anatomical structure of upper airways.[374] Young and colleagues[360] investigated the predictors of SDB in a representative sample of 5,615 adults aged 40 to 98 years. They reported that there is ageing is positively associated with OSA, and 65 years of age was found to be a plateau for these associations.

4.2.1.4.2 Gender

A great number of epidemiological studies have previously suggested that the prevalence of OSA is approximately 1.5 to 3 times higher in men than in women.[105] Although the exact mechanism of gender impact on OSA is not clear, there are several hypotheses that may potentially explain the male preponderance. The characteristics of OSA symptoms have been reported to differ between men and women.[247] Women are less likely to report snoring as a symptom and are more likely to report other symptoms such as headache and other sleep problems and in some cases depression, which can increase the risk of receiving treatment for depression rather than OSA. Undiagnosed OSA among women may impact mortality, as results from a study by Young and Finn[152] showed that the proportion of deaths in women with AHI of ≥ 5 events/hour was higher compared to men (n = 354, 27% (3/11) vs. 2% (1/49), women vs. men respectively). There are other explanations such as the difference in the anatomical structure of upper airways in men and women.[375] Although women have smaller upper airways and might be expected to be at higher risk of developing OSA, interestingly men have longer airways which are more susceptible for collapse.[375] The results of imaging studies suggest that the distribution of fat is different in men and women, as there is more fat tissue around the pharyngeal area in men, whereas in women, the fat is distributed at lower part of the body.[375]

4.2.1.4.3 Ethnicity

Since the consequences of untreated OSA and its related adverse health complications such as cardiovascular diseases were appreciated, several studies have been conducted in America, Europe, Asia, and Australia to characterise the disease burden in those regions (Table 4-3). Evidence indicates that the prevalence of OSA in China[364, 365] and Korea[366] may be comparable with that in the US,[360, 361] Spain[362] and Australia,[367] but

the prevalence of the disease is higher in India[363] compared to those regions. In a recent population-based study, Leong and colleagues[376] compared the prevalence of OSA between South Asians and white Europeans with a total of 308 participants (mean (SD) age: 46 (12) years, and mean (SD) BMI: 49 (8) kg/m^2). The findings showed that South Asians had an increased prevalence of OSA compared to white Europeans (85% vs. 66%, p = 0.017). The severity of the OSA is higher in South Asians.[358] Leong and colleagues[376] reported that in their sample, South Asians were more likely to suffer from severe OSA (AHI ≥30 events/hour) (42.5% vs. 21.6%, p = 0.015) compared to white Europeans. This study, however, was carried out in individuals with extreme obesity and may not be applicable to other groups.

There is a limited data on prevalence of OSA among Hispanics. It was previously found that the prevalence of the disease in African-American middle-aged adults is comparable to other ethnic groups.[377] However, younger African-American adults (<25 years old) had a higher prevalence of the disease compared to African-American middle aged adults or Chinese or Caucasians.[377]

There are differences in the prevalence and severity of OSA among different ethnic group. The mechanism mediating the observed associations require further investigation, but may include body fat distribution, craniofacial anatomical differences and variations in the control of breathing.

4.2.1.4.4 Overweight/obesity

The prevalence of obesity is increasing worldwide. Epidemiological studies consistently suggest excessive body weight is prevalent in approximately 60% of people that have been diagnosed with OSA.[105] Evidence indicates that an increase in

measures of body habitus (BMI, neck circumference, or waist-to-hip ratio) could potentially result in an increase in the prevalence of OSA (Table 4-4).

Table 4-4. Prevalence of OSA by BMI in several population-based studies.[378]

Authors and year	Country	Sample	AHI (events/hour)	BMI (kg/m^2)	Prevalence of OSA (%)
Bixler et al, 1998, 2001[361, 374]	United States	1,000 F, 741 M, 20 – 100 years	≥15, Laboratory PSG	F, <32.3	1.1
				≥32.3	7.2
				M, <32.3	2.0
				≥32.3	13.8
Young et al, [379] 2002	United States	5,616 M,F 40 – 98 years	≥15, Home PSG	Quartiles:	
				16-24	10
				24-48	13
				28-32	17
				32-59	32
Ip et al,[364, 365]2001, 2004	Hong Kong	106 F, 153 M, 30 – 60 years	≥5, Laboratory PSG	F, <23	0.9
				≥23	14.5
				M, <23	0.9
				≥23	8.8

Apnoea Hypopnoea Index (*AHI*), Body Mass Index (*BMI*), Obstructive Sleep Apnoea (*OSA*), Male (*M*), Female (*F*).

Used with the permission from Dr Young.

Excessive body weight is highly contributory to the increase the prevalence of OSA, as each unit increase in BMI could potentially increase the risk of development of OSA by 14% (95% CI 1.10 – 1.19). However, the impact of BMI on OSA is less significant among older individuals (>60 years).[372]

As stated earlier, changes in body weight could increase or decrease OSA. Body weight gain by %10 among individuals with no OSA or mild OSA (<15 events/hour) was associated with a 32% (95% CI 20% – 45%) higher risk of developing or worsening of OSA (AHI ≥15 events/hour). Additionally, a 10% weight loss was associated with a 26% (95% CI 18% - 34%) decrease in severity of OSA.[161]Simarly, results from the Sleep Heart Health Study,[371] involving 5-year evaluation of weight

changes among 2,968 men and women aged 40 to 95 years showed that effects of weight gain on an increase in AHI is much stronger than the effects of weight loss on a decrease in AHI. For example, in men, a 10 kg weight gain was associated with an odds ratio of 5.21 (95% CI 2.35 – 11.53) for progression of AHI of >15events/hour, while the odds ratio of 10 kg weight loss for a decrease in AHI by 15 event/hour was 2.85 (95% CI 1.28 – 6.31).[371] Due to the lack of observational and randomised controlled studies on the effect of weight loss (via either surgery or lifestyle modification) on treatment of OSA, it is difficult to draw concrete conclusions as to whether a reduction in weight can be known as a curative method for treatment of OSA.

Despite the cumulative evidence suggesting that obesity is an important risk factor for OSA, it is largely unknown that whether it is central or peripheral distributions of fat that are associated with a greater risk of having OSA. It can be argued that such a challenge to findings answer to the above question may be due to limitations of current measures of obesity as described in *Chapter 1*. Waist and neck circumferences were found to be significantly associated with AHI.[360] It can be explained that changes in waist and neck circumferences are highly correlated with changes in total body weight, and weight loss would also reflect reductions in waist and neck circumference. Breathing may be influenced by excessive body weight through several mechanisms: 1) alterations of upper airway structure by increased fat deposition around the neck area, 2) decreased neural compensatory mechanisms to signal greater respiratory effort and increased susceptibility of airways to be blocked, 3) instability of respiratory control system, and 4) instability of caudal tracheal traction that ordinarily assists in airway patency as a result of reduced functional residual capacity (the volume of air in the lungs after normal expiration).[163] It appears that weight gain may increase the risk

of developing of OSA, and also worsen the condition among those who have already been affected.

Public health strategies with a focus on long-term weight loss are favoured to tackle the epidemics of both obesity and OSA.

4.2.1.4.5 Genetics

The role of genetics on the development of OSA was first suggested by Strohl and colleagues when they observed the clustering of OSA within the same family.[380] Since then, numerous epidemiological studies have suggested that individuals with a family history of OSA are at higher risk of developing the disease.[163] An increase in number of relatives with OSA may be associated with higher risk of OSA in an individual.[381] It has been highlighted that familial connections in weight and craniofacial morphology may also increase the risk for development of OSA.[163] Findings from Cleveland Family Study[163] showed that independent of obesity, 35% of variance in the AHI could be explained by genetic factors. The susceptibility of OSA as a result of genetic factors may differ between ethnic groups.[382] It has been argued that confounder variables and in particular obesity may mediate the association causality between genetic factors and OSA, therefore future studies are needed to confirm the independent familial predisposition.

4.2.1.4.6 Craniofacial anatomy

Evidence indicates that there is a difference in skeletal and soft-tissue structural differences among OSA and non-OSA patients.[383] Craniofacial abnormalities including mandibular deficiency, enlarged soft plate, decreased posterior air space and tonsillar hypertrophy may narrow the upper airway dimension and yield apnoea and hypopnoea events.[383] The results of a systematic review demonstrated that mandibular

length was associated with increased risk of OSA and a slight difference in mandibular size may result in development of the condition, even in the absence of distinct craniofacial deformity.[384] Interestingly, craniofacial morphology may differ among different ethnic groups. Evidence indicates that the association between AHI and measurements of the soft palate was stronger in African Americans compared to Caucasions.[385] Similar studies[386, 387] have been conducted among Chinese and Asian individuals and their results revealed that independent of obesity measures (e.g. BMI and neck circumference) Chinese OSA patients had more mandibular retrognathia (retracted mandible) compared to their matched white controls. Moreover, Asians have a shorter cranial base, which may increase their vulnerability to develop the disorder. Craniofacial anatomy is an important risk factor for OSA, particularly in lean individuals. Evaluation for OSA in presence of apparent anatomical abnormalities may lead to early detection of the disorder and prevention of further health consequences.

4.2.1.4.7 Smoking and Alcohol consumption

It has been hypothesised that smoking may affect OSA through sleep instability and airway inflammation.[388] Numerous cross-sectional studies have previously reported that there is a positive link between cigarette smoking and OSA.[389, 390] Current smokers are three times more likely to have OSA compared never smokers (95% CI, 1.4 - 6.4).[391] Interestingly, the prevalence of the disease did not significantly differ between former smokers and never smokers, which suggesting that smoking cessation, could potentially reduce the risk of OSA. [391] In a longitudinal study, Lindeberg and colleagues[389] found that smoking was a strong predictor for snoring among young adults (aged <60 years old) (OR 1.4, 95% CI 1.1 - 1.9). Unexpectedly, analysis of data from the Sleep Heart Health Study demonstrated that there is a negative link between current smoking and OSA following adjustment for age and BMI.[390] The authors

suggested that the observed inverse association may be due the fact that individuals with severe OSA are more likely to quit smoking. However, there was no significant association between former smoking status and OSA. Data on the biological plausibility of smoking and OSA are lacking, therefore future studies are needed to address this.

Nasal and pharyngeal resistance are found to be associated with alcohol ingestion during wakefulness: therefore it can be hypothesised that alcohol may disrupt respiratory patterns during sleep during sleep.[392] To date, the majority of experimental[393-395] and epidemiological studies[394, 396] found a positive association between alcohol consumption and OSA. Alcohol may result in pharyngeal collapsibility, prolonged apnoeas, more frequent hypopnoeas and increased frequency of hypoxaemia.[394] Moreover, alcohol is a muscle relaxant that may affect the muscular mechanisms of airway patency. In general, studies have evaluated the acute effects of alcohol on sleep and little is known about its longer-term effects. In the WSCS, Peppard and colleagues[397] evaluated the long-term effect of alcohol consumption on sleep and they reported that excessive alcohol intake was strong predictor for mild to severe OSA (OR 1.25, 95% CI 1.07-1.46). Future studies are needed to confirm these findings.

4.2.1.5 Consequences of untreated OSA

Despite the fact that OSA was first recognised almost 35 years ago, data on the prevalence of OSA were markedly lacking until a decade ago. It is estimated the prevalence of undiagnosed OSA would differ between 0.3 to 5%.[105] Under-recognition of the disorder in both public and clinical settings may lead to multiple adverse health outcomes. Some of the main consequences of untreated OSA such as

cardiovascular morbidity and mortality, diabetes and sleepiness are discussed as below.

4.2.1.5.1 Cardiovascular morbidity and mortality

It was previously found that apnoea and hypopnoea events may result acute rise in mean arterial pressure by 30 mmHg or even higher during sleep.[398] Results from epidemiological evidence suggests that OSA may increase the risk for hypertension independent of obesity and other potential confounders, as I have reported earlier.[399]

Population-based cross-sectional data using both objective measures of OSA and self-reported snoring report positive associations between OSA and with cardiovascular disease (CVD). In the Sleep Heart Health Study involving 6,424 participants, Shahar and colleagues[400] found that the risk for CVD was (OR 1.42, 95% CI 1.13 - 1.78) higher among those in the upper quartile of AHI (≥11 events/hour) compared to those in the lowest quartile (<1.3 events/hour) following multivariate adjustment for potential confounders. Results from case-control evidence have demonstrated that OSA may increase the risk of myocardial infarction (MI) by up to 4-fold among men and women.[401] It appears that the link between stroke and OSA is stronger than the link between CVD and OSA.[402] However, alterations in cardiac output and medication following MI may affect the severity of OSA.[403] Longitudinal studies that have assessed the possible link between OSA and CVD have also confirmed the observations from cross-sectional studies.[402] Using data from Nurses' Health Study, Hu and colleagues[402] reported that self-reported snoring was a strong predictor for incidence of CVD among 72,000 women across 8-year follow-up period (OR 1.33, 95% CI 1.06 – 1.67).

It has been previously hypothesised that OSA may lead to cardiovascular morbidity and mortality through several mechanisms including atherosclerosis as a result of hypoxaemia and sympathetic hyperactivity, increased blood pressure, rise in fibrinogen, and increased risk for heart failure.[398] Evidence indicates that treatment of OSA may also help to reduce blood pressure.[404] Results of a recent systematic review and meta-analysis including 28 studies which represented of 1,948 participants showed that CPAP did result in a significant decrease in diurnal systolic (-2.58 mmHg, 95% CI -3.57 to -1.59 mmHg) and diastolic (-2.01 mmHg, 95% CI -2.84 to -1.18 mm Hg) blood pressure compared to controls.

Epidemiological evidence have suggested that OSA may potentially increase CVD mortality.[405] Lindberg and colleagues[405] have assessed the potential link between snoring and excessive daytime sleepiness and mortality over a 10-year follow-up. They could not find any significant association between snoring and mortality across the whole sample, but in a subgroup of men aged 60 years and younger, those who reported snoring with excessive daytime sleepiness were twice likely to die over the course of the study, compared to those who were symptoms free (OR 2.2, 95% CI 1.3 – 3.8). In similar studies involving less than 200 older participants, Bliwise and colleagues[406] and Mant and colleagues[407] did not detect any statistically significant relationships between age-adjusted cardiovascular mortality and OSA. It is possible that compared to younger individuals, less noxious feature of OSA would be present in older individuals or older individuals are more resistant to adverse consequences of OSA. In general, individuals with untreated OSA may be at higher risk for early death. Future studies with objective measures of OSA are needed to quantify the magnitude risk of OSA on cardiovascular morbidity and mortality.

4.2.1.5.2 Diabetes

Type 2 diabetes could be another consequence or another chronic condition associated with untreated OSA. West and colleagues[408] reported that the prevalence of OSA was higher in diabetes population (23% vs. 6%, $p<0.001$, diabetics vs. non-diabetics respectively). Numerous cross-sectional and a few longitudinal studies have previously investigated the link between OSA and type 2 diabetes. In some studies, the presence of OSA was assessed by PSG and in some others it was assessed using self-reported snoring. Cross-sectional studies that used PSG to assess OSA consistently reported that OSA was associated with an increased risk of diabetes. Using data from 2,656 participants in the Sleep Heart Health Study, Punjabi and colleagues[409] found that higher AHI and ODI were associated with an increased risk of glucose intolerance and insulin resistance measured by an oral glucose tolerance test. This association was independent of body mass index and other potential confounders (OR 1.46, 95% CI 1.09 - 1.97). Results from the Cleveland Family study showed that individuals with OSA that had spent 2% time in saturation level of <90% had an increased risk for impaired glucose tolerance (OR 2.33, 95% CI 1.38 - 3.94).[410] The results from the only longitudinal study that assessed OSA using overnight polysomnography did not find an independent association between OSA and the incidence of diabetes following 4-year follow-up period.[411] Findings from studies that explored the potential link between snoring and the parameters of glucose tolerance also suggested that there is a positive association between these phenomena.

Data on causal role of OSA in the progression of type 2 diabetes is lacking and it is hypothesised that OSA can lead to abnormalities in glucose metabolism through various mechanisms including: increased activity of sympathetic nervous system, hypoxaemia, endothelial dysfunction, sleep fragmentation, alteration in cytokines, and

dysregulation of the hypothalamic-pituitary axis.[412] For examples, increased sympathetic nervous system and release of hormones counter-regulatory to insulin, could affect glucose homeostasis.[412] Also, hypoxaemia, has been associated with abnormalities in insulin secretion from pancreatic beta cells.[412]

4.2.1.5.3 Daytime sleepiness

Excessive daytime sleepiness is a key feature of OSA, giving the full obstructive sleep apnoea "syndrome". The possible link between OSA and sleepiness is poorly understood, but current evidence has confirmed the causal role of OSA and non-apnoeic snoring in occurrence of sleepiness.[413] Repeated arousals from apnoeas and hypopnoea result in sleep fragmentation during the night, which could lead to daytime sleepiness the next day. Results from the Sleep Heart Health Study[414] demonstrated that there is a positive association between the total score of the Epworth Sleepiness Scale (ESS) and RDI, independent of age, gender, race, BMI, and insufficient sleep time (ESS, mean (SD) RDI<5 events/hour 7.2 (4.3) vs. 9.3 (4.9) RDI≥30 events/hour). Stradling and colleagues[413] found that habitual snoring independent of the severity of OSA could potentially increase the risk of daytime sleepiness by 5-fold (95% CI 2.7 - 12.5). Findings from several other epidemiological studies,[360, 414] have confirmed that snoring even in absence of evident apnoea and hypopnoea events can increase the risk for daytime sleepiness, although the underlying mechanisms are not fully understood as there might be some potential confounders such as voluntary sleep restriction, although one study reported that the positive association between snoring and daytime sleepiness is independent of voluntary sleep restriction.[415]

Numerous studies suggest that motor vehicle accidents are prevalent among OSA patients and that these individuals also suffer from poor performance while driving on

the road.[171] Using data from Wisconsin Sleep Cohort Study, Young and colleagues[171] found that only among males, those with AHI ≥5 events/hour or habitual snorers were more likely to have at least 1 road accident in a 5-year period compared to those with AHI <5 events/hour or non-habitual snorers. It is believed that sleepiness may explain the link between OSA and increased risk for work and road accidents. However, recent findings showed that the association between OSA and motor vehicle accidents is independent of sleepiness.[416] A Swedish cohort study,[389] involving 2,724 male participants, found that OSA patients or heavy snorers had higher risk for occupational accidents in a 10-year period (OR 2.2, 95% CI 1.3 - 3.8). The economic burden of OSA is substantial.[417] It is known that OSA is associated with OSA-related accidents cost approximately $15.9 billion annually and medical treatment can markedly reduce this cost by up to $11.1 billion.[417]

4.2.1.6 Treatment

Continuous positive airway pressure (CPAP) is the gold standard treatment for OSA.[105] CPAP usually delivers a pneumatic splint to the airway during expiration. More complex patients may require bi-level treatment with pressure delivered during both inspiration and expiration. CPAP reduces AHI and may also reduce OSA associated morbidities, in particular cardiovascular events mortality. In a long-term follow-up study, Doherty and colleagues[418] evaluated the impact of CPAP therapy on cardiovascular outcomes of 168 OSA patients, who had received CPAP treatment for 5 years prior to the study. After 7.5 years follow-up, those patients who were intolerant of CPAP (n = 61) had higher AHI compared to those continuing the therapy (48.3 events/hour vs. 36.7 events/hour, respectively; p = 0.02). Death from cardiovascular disease was significantly higher among those who were CPAP intolerant compared to CPAP adherent group (14.8% vs. 1.9%, respectively; p = 0.009).

Overall, almost a quarter of patients have difficulties tolerating CPAP therapy.[419] Studies have demonstrated that CPAP treatment cannot always alleviate OSA symptoms such as daytime sleepiness.[419] Given that best CPAP usage is between 4-5 hours per night, it is likely that OSA patients on CPAP still continue to have hypoxaemia and sleep disruption for the remainder of the night. Compared to CPAP, oral appliances and surgery are less effective and maybe successful in only a small proportion of patients.[420] Oral appliances (OA) are another treatment method for OSA and they may reduce the collapsibility of upper airways by enlarging the airways and keeping them patent.[421] Although OAs are not as effective as CPAP, they are usually recommended in patients who did not respond to other treatment methods such as CPAP or lifestyle interventions.[421] Surgery is also used for the treatment of OSA. Surgical procedures are reversed for extreme cases and may result in complications and side-effects such as bleeding and infection.[422] Pharmacotherapy has been employed effectively to improve daytime sleepiness in OSA, but is unlikely to improve the cardiovascular problems that accompany it. Given the issues with current treatment methods, and the important association between OSA and obesity, lifestyle change with weight reduction is a common clinical recommendation by several guidelines.[423]

Regardless of benefits of weight loss on reducing AHI,[161] it is has been hypothesised that OSA per se may increase the risk for obesity with several potential mechanisms.[424] Sleep fragmentation as a result of OSA is highly correlated with excessive daytime sleepiness which may preclude OSA patients from carrying out physical activity that may translate to greater obesity.[424] West and colleagues, however, found that even after CPAP therapy and elimination of sleepiness, the physical activity levels of OSA patients did not increase.[425] Another mechanism through which OSA could predispose

to obesity is loss of sleep and poor sleep quality, which have been associated with increased body weight. Other mechanisms are discussed below (see discussion).

It is generally recommended that obese OSA patients reduce weight through diet and exercise programmes or a mixture of both. It has been previously found that weight loss via a very low calorie diet (VLCD) can markedly reduce AHI. Increase in physical activity levels can also reduce AHI severity.[424] The most common form of exercise employed in research studies on obese OSA patients is aerobic exercise.[424]

4.2.2 Lifestyle interventions for OSA: mechanisms

It is well known that obesity is a major risk factor for sleep apnoea. Epidemiological evidence indicates that OSA is highly prevalent among the obese population, and the majority of OSA patients are obese.

Results from a recent published meta-analysis[426] of 12 studies representing 342 patients suggested that bariatric surgery could potentially reduce the severity of OSA in a sample of individuals with extreme obesity. The random-effects pooled baseline apnoea hypopnoea index of 54.7 events/hour (95% CI, 49.0 - 60.3) was reduced by 38.2 events/hour (95% CI, 31.9 - 44.4) to a final value of 15.8 events/hour (95% CI, 12.6 - 19.0). Evidence from lifestyle interventions such as diet and increased physical activity levels showed a reduction in AHI. [424, 427] Moreover, it has been found that weight loss could reduce upper airway collapsibility and increase several measures of lung function including vital capacity, functional residual capacity, forced expiratory volume and total lung volume (see appendix regarding lung volume).[428] There are some unaddressed issues regarding the effect of weight loss on OSA. For instance, the amount of weight loss that requires producing significant improvement in OSA and

associated symptoms (e.g. daytime sleepiness) is yet to be confirmed. Data on weight loss sustainability and longer-term effects of lifestyle intervention on OSA are lacking.

Compared to other treatment options and at first consideration, lifestyle weight loss interventions are likely to be cheaper and more feasible, but their effectiveness has not been assessed systematically. These interventions can be used mutually with CPAP. A decrease in severity of OSA through lifestyle modification intervention may improve CPAP adherence through a potential reduction of applied expiratory pressures required to maintain airway patency.

4.2.3 Aims

Although several treatment options are available for OSA patients, not all patients adhere to or respond well to options such as CPAP and oral devices. On the other hand, surgical options are associated with a higher risk of adverse outcomes.[422] Lifestyle modification strategies such as weight loss through diet and exercise or their combination may be an attractive alternative treatment option. These approaches are also generally recommended to patients, but are not systematically addressed.

Given the recommendation of lifestyle interventions for the treatment of OSA, a systematic review and meta-analysis was conducted to examine the available evidence for this. I sought to assess the effectiveness of lifestyle interventions on reducing the severity of OSA. In particular, I was interested in determining the mean changes in AHI and oxygen desaturation index of 4% (ODI) following termination of lifestyle interventions. Additionally, I also assessed the impact of these interventions on common symptoms of OSA such as daytime sleepiness.

4.2.4 Hypothesis

The systematic review aimed to assess the effectiveness of lifestyle interventions on the severity of OSA. In particular, it was hypothesised that the mean change in AHI and oxygen desaturation index of 4% (ODI) would significantly vary from baseline to post lifestyle intervention.

4.3 Methods

4.3.1 Data sources and searches

Study protocol was registered with International Prospective Register Of Systematic Reviews (PROSPERO) (Registration Number: CRD42011001511).[429]

A systematic search was performed to identify relevant publications using Medline (from 1948), Embase (from 1988), CINAHL (from 1983), Opengrey, OAIster, Zetoc, BioMed Central, NLM Gateway, Cochrane Library, ISRCTN, and www.clinicaltrials.gov (from database inception to April 2011). Reference lists and unpublished studies were also checked. In order to formulate the search strategies, the record of exact search terms and their results were kept to refine the final search strategy. The search terms were ("obstructive sleep apnea" or "obstructive sleep apnoea" or "sleep disordered breathing") and ("lifestyle" or "exercise" or "weight loss" or "weight" or "diet" or "physical activity")

4.3.2 Study selection

To be eligible for inclusion, research papers had to report data on adult patients (≥18 years old; male and female) with confirmed diagnosed OSA (AHI ≥5 events/hour or ODI4 ≥5 episodes/hour) and investigated lifestyle modification interventions (defined as a comprehensive program of diet and/or exercise therapy[430] without treatment with CPAP at the start of the intervention). Surgical and pharmacological interventions were excluded. Randomised and non-randomised studies that compared a lifestyle modification intervention with no intervention, usual care or placebo were eligible for inclusion. Uncontrolled before-and-after studies were also included to provide supportive evidence given the small number of comparative studies identified.

Based on the above inclusion criteria, titles and abstracts were screened independently by two members of the research team (AJ, SC) with access to full-text where necessary to select studies to include in the review. Disagreements on inclusion decisions were resolved by discussion.

4.3.3 Data extraction and quality assessment

A standardised form was used to extract data on the descriptive findings including; patients' demographic and clinical characteristics, length of weight loss intervention, length of follow-up, and change in body mass index (BMI), change in AHI, and change in ODI4 pre- and post- intervention and been checked for accuracy by AJ and SC. Additional information from each study was also obtained on the first author's last name, year of publication, country where the study was done, study name, and sample size. Authors were contacted to provide requested data.

The methodological quality of the included randomised controlled studies was assessed using Cochrane risk of bias tools. These studies were assessed for random sequence generation, allocation concealment, blinding (as the blinding of the participants is not possible for such interventions, blinding of statistician), incomplete outcome data, selective outcome reporting and any other biases (Table 4-5). The methodological quality of uncontrolled before-and-after studies was assessed using relevant items from the Cochrane Effective Practice and Organisation of Care Group (EPOC) risk of bias tool for interrupted time series studies and items used by Chambers and colleagues[431] for assessing case series (Table 4-6).

4.3.4 Data synthesis and analysis

Outcomes (AHI, ODI4, BMI, ESS) were combined using the random effects model of DerSimonian and Laird,[432] and expressed as weighted mean differences. Randomised controlled trials (RCTs) and uncontrolled before-and-after studies were analysed separately. For randomised controlled studies, data included in the analysis were the change from baseline to post- intervention between intervention and control groups.

For uncontrolled studies, the data analysed were the changes post intervention compared to baseline for a single group. In the latter analysis because ODI4 was the outcome, data from the intervention arm of one RCT[433] was regarded as an 'uncontrolled before-after studies' and was also included. The meta-analysis was performed using RevMan 5.1 (Update Software, 2011). In order to weight the studies, an inverse variance method was used.[434] Meta-regression was carried out using restricted maximum likelihood estimators (REML) to examine the coefficient of variability between reduction of weight and change in AHI and also between baseline AHI and change in AHI. I assessed the presence of potential publication bias using Dear and Begg's test[435] and results were obtained from using the "selectMeta" package in R.[436] Statistical heterogeneity was assessed using the chi-square statistic and the I^2 statistic, with I^2 greater than 50% indicating at least moderate heterogeneity. A p-value less than 0.05 was considered to be statistical significance.

4.4 Results

4.4.1 Study characteristics

A total of 3,837 references were retrieved by the search. The flow of the studies is shown in Figure 4-3. A review of the titles allowed for the exclusion of 3,791 publications. I reviewed the full-text of 46 studies that were potentially suitable for inclusion in the meta-analysis. After excluding duplicate studies and those that did not meet the inclusion criteria, 21 studies representing 893 patients were identified for inclusion. Seven randomised controlled trials[424, 427, 437-441] with a total of 519 participants and fourteen uncontrolled before-and-after studies[428, 433, 442-453] with a total number of 374 participants were included. All studies assessed the effect of weight loss through lifestyle modification interventions such as diet, exercise or using both methods on patients with OSA. The length of the intervention varied from 4 weeks to 24 months. Descriptive data for the included studies are presented in Table 4-7 and Table 4-8.

Most studies were performed in Finland and the Unites States. The rest of the studies were from Sweden, Spain, Australia, Canada and Brazil. The sample size varied from 8 to 264 individuals with an average age of the participants being 49 years. Despite attempts to contact authors to provide additional unpublished data, I could not find information describing changes in BMI for one randomised controlled study.[438] With the agreement of all the co-authors, the observational study by Johansson and colleagues[445] was recognised as an independent study from their previous randomised controlled study and was eligible for inclusion.[427]

A very low calorie diet (VLCD) (intake <800 $kcal \cdot d^{-1}$) intervention was used by thirteen studies.[427, 433, 438, 439, 441, 443-445, 447-449, 451, 454] Four studies used combined interventions [437, 442, 446, 452] including VLCD with either exercise or cognitive behavioural therapy. An exercise intervention was used by four studies.[424, 440, 450, 453] Five studies reported ODI4 as the outcome measure [433, 443, 446-448]; six studies reported both AHI and ODI4,[424, 427, 428, 437, 445, 449]and ten studies only reported AHI as the outcome.[438, 439, 441, 442, 444, 445, 450-453]

The baseline BMI average varied from 29.0 to 54.6 kg/m^2. For the sleep outcome, AHI varied from 10 to 66.5 events/hour and for ODI4 varied from 30 to 51 events/hour.

Table 4-5. Quality assessment of randomised controlled trials.

	Sequence Generation	Allocation concealment	Blinding	Incomplete outcome data	Selective outcome reporting	Free from other bias
Kajaste et al 2004[433]	Low Risk	Unclear	Unclear	Low Risk	High Risk	Unclear
Habdank et al 2006[438]	Unclear	Unclear	Unclear	High Risk	High Risk	Unclear
Kemppainen et al 2008[439]	High Risk	Unclear	Unclear	Low Risk	Low Risk	High Risk
Johansson et al 2009[427]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Sleep AHEAD 2009[455]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear
Tuomilehto et al 2009[441]	Low Risk	Low risk	Unclear	Unclear	Low Risk	Unclear
Kline et al 2011[424]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear
Sengul et al 2011[440]	Low Risk	Unclear	Unclear	Low Risk	Low Risk	High Risk

Table 4-6. Quality assessment of uncontrolled before-after studies.

	Suratt et al[428] 1987	Pasquali et al[451] 1990	Kajaste et al[446] 1994	Hakala et al[443] 1995	Lojander et al[448] 1998	Sampol et al[452] 1998	Kansanen et al[447] 1998	Norman et al[450] 2000	Ueno et al[453] 2009	Barnes et al[442] 2009	Hernandez et al[444] 2009	Nerfeldt et al[449] 2010	Johansson et al[445] 2011
1. Were selection/eligibility criteria adequately reported?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Was the selected population representative of that seen in normal practice?	Unclear	Unclear	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3. Were patients recruited prospectively?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4. Were patients recruited consecutively?	Unclear	Unclear	Yes	No	No	No	No	No	Yes	Yes	Yes	Yes	Yes
5. Did the study report relevant prognostic factors?	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	No	Yes	Yes	Yes	Yes
6. Was the intervention independent of other changes?	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes	Yes
7. Was the intervention unlikely to affect data collection?	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes	Yes
8. Were objective outcomes used or were outcomes assessed blindly?	Yes	Yes	Unclear	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear
9. Were incomplete outcome data (missing data or loss to follow-up) adequately addressed?	Yes	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes
10. Was the study free from selective outcome reporting?	Unclear	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Yes
11. Was the study free from other risks of bias?	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Unclear	Yes	Yes

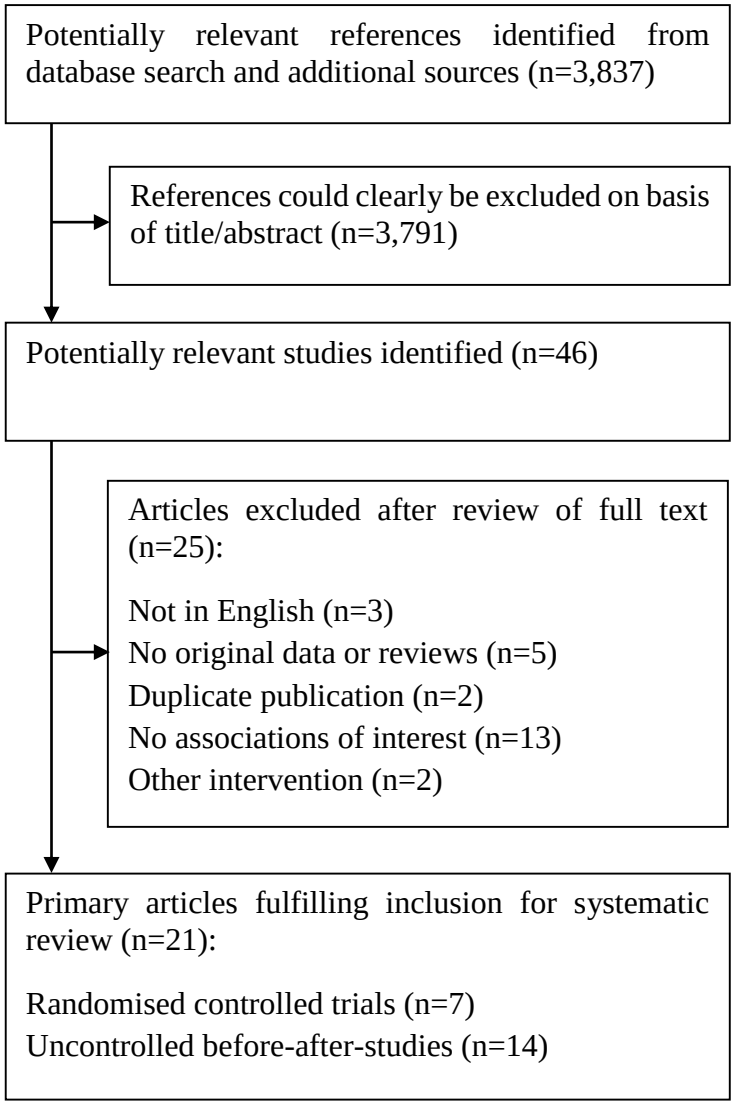

Figure 4-3. The flow diagram describes the flow of information through the various stages of the systematic review.

Table 4-7. Key characteristics of included trials.

Trial	Location	Design	Size	Length of intervention	Length of follow-up	Intervention	Key findings
Suratt et al 1987[428]	USA	Prospective observational	8	4 weeks	NR*	Diet	A great reduction in number of apnoeas and hypopnoea was observed among eight OSA patients. BMI was found to be highly correlated with AHI
Pasquali et al 1990[451]	Italy	Prospective observational	23	6 months	NR	Diet	Weight loss was associated with a significantly reduction in AHI. Weight loss was an important predictor of change in total number of apnoeas and hypopnoea events
Kajaste et al 1994[446]	Finland	Prospective observational	32	6 months	12 months, 24 months	Cognitive-behavioural (encouraging low calorie diet)	At 12-month follow-up there was a significant improvement in ODI4. At 2-year follow-up both BMI and ODI4 were lower compared to baseline which demonstrated that the participants were enthusiastic to sustain to the changes
Hakala et al 1995[443]	Finland	Prospective observational	13	6 weeks	NR	Diet	Rapid weight loss was observed following the utilisation of VLCD programme. There was a strong correlation between BMI and ODI4. Seven out of thirteen OSA patients achieved normal ODI4 after six weeks dietary weight loss intervention
Lojander et al 1998[448]	Finland	Prospective observational	24	6 weeks	1 year	Diet	A nurse-managed dietary weight loss programme is relatively safe and cheap method to normalise sleep among OSA patients. No link was found between weight loss and ODI4 improvement
Sampol et al 1998[452]	Spain	Prospective observational	67	NR	2 years	Diet+ Exercise	Mixed programme of dietary and physical activity weight loss interventions were associated with a significant reduction in AHI. OSA patients were also benefited the intervention in long term
Kansanen et al 1998[447]	Finland	Prospective observational	18	3 months	NR	Diet	Lifestyle weight loss through dietary intervention can be considered as an effective method to normalise sleep in obese OSA patients. Weight loss had a positive impact on blood pressure and baroreflex

Table 4-7 cont'd

Trial	Location	Design	Size	Length of intervention	Length of follow-up	Intervention	Key findings
Norman et al 2000[450]	USA	Prospective observational	11	6 months	NR	Exercise	Regular exercise training had a positive impact on the AHI
Kajaste et al 2004[433]	Finland	Randomised controlled trial	31	6 weeks	6 months, 12 months, 24 months	Diet	At 6-month follow-up, the mean reduction of weight loss was 19 kg and at 2-year follow-up was 13 kg which demonstrated that the participants were enthusiastic to sustain to the changes
Habdank et al 2006[438]	Canada	Randomised controlled trial	18	6 months	NR	Diet	Compared to usual care, the dietary intervention did not result in greater weight loss or improved AHI
Kemppainen et al 2008[439]	Finland	Randomised controlled trial	52	3 months	NR	Diet	The intervention program achieved a significant reduction in BMI and AHI. There were no significant changes in rhinometric measurement
Ueno et al 2009[453]	Brazil	Prospective observational	25	4 months	NR	Exercise	No change was observed in anthropometric measurements, although exercise programme could potentially lessen the severity of OSA and improve neurovascular function, quality of life and functional capacity
Barnes et al 2009[442]	Australia	Prospective observational	12	16 weeks	12 months	Diet + Exercise	A combined programme of dietary and physical activity programme was associated with significant improvement sleep apnoea, as well as cardiometabolic outcomes
Johansson et al 2009[427]	Sweden	Randomised controlled trial	63	9 weeks	NR	Diet	Weight loss via VLCD resulted a significant reduction in AHI among obese men
Hernandez et al 2009[444]	USA	Prospective Observational	14	6 months	NR	Diet	A significant reduction was observed in AHI between pre and post weight loss intervention. Patients with severe OSA at baseline had benefited the most from the intervention

Table 4-7 cont'd

Trial	Location	Design	Size	Length of intervention	Length of follow-up	Intervention	Key findings
Sleep AHEAD 2009[437]	USA	Randomised Controlled Trial	264	1 year	NR	Diet + Exercise	It has been found that baseline AHI was a strong predictor of AHI reduction following a dietary weight loss intervention. It was also observed that OSA patients that could achieve weight reduction of 10 kg had better improvement in AHI
Tuomilehto et al 2009[441]	Finland	Randomised controlled trial	59	10 weeks	3 months, 12 months	Diet	The lifestyle weight loss intervention was associated with significant improvement in AHI. A dose-response trend was found between weight and AHI
Nerfeldt et al 2010[449]	Sweden	Prospective Observational	33	8 weeks	2 years	Diet	The dietary weight loss programme resulted significant improvement in reducing AHI as well as weight, ODI, and subjective symptoms
Kline et al 2011[424]	USA	Randomised controlled trial	43	12 weeks	NR	Exercise	AHI was significantly reduced following an aerobic exercise intervention. In contrast no reduction in weight and BMI was observed may also indicate that the association between weight loss and AHI improvement may goes beyond weight loss
Sengul et al 2011[440]	Turkey	Randomised controlled trial	20	12 weeks	NR	Exercise	The anthropometric characteristics of patients with mild to moderate OSA did not change after completion of exercise intervention, while significant improvement was ascertained in AHI, quality of sleep, quality of life
Johansson et al 2011[445]	Sweden	Prospective Observational	63	9 weeks	1 year	Diet	Weight loss maintenance was achieved flowing 1-year follow-up. OSA patients with severe AHI had attained greater reduction in AHI

Table 4-8. Key characteristics of study participants.

Trial	Sex	Age (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/hour)	AHI after intervention (events/hour)	ODI4 at baseline (episodes/hour)	ODI4 after intervention (episodes/hour)
Suratt et al 1987[428]	M/F	48	153.0	134.7	54.6	45.9	25.3	22.7	33.0	20.1
Pasquali et al 1990[451]	M/F	46	105.1	86.7	37.5	30.9	66.5	33.0	NR	NR
Kajaste et al 1994[446]	M/F	48	NR	NR	38.5	35.0	NR	NR	38.6	23.9
Hakala et al 1995[443]	NR	NR	111.0	95.0	35.0	31.8	NR	NR	31.0	10.0
Lojander et al 1998[448]	M	49	110.0	97.0	36.0	31.0	NR	NR	30.0	13.0
Sampol et al 1998[452]	M/F	53	NR	NR	31.5	25.9	52.3	44.2	NR	NR
Kansanen et al 1998[447]	M/F	52	114.0	105.0	38.1	35.1	NR	NR	31.0	19.0
Norman et al 2000[450]	M/F	48	110.9	104.7	31.2	29.6	21.7	11.8	NR	NR
Kajaste et al 2004[433]	M/F	50	140.0	121.0	43.8	37.8	NR	NR	51.0	23.0
Habdank et al 2006[438]	M/F	50	NR	NR	NR	NR	26.3	34.3	NR	NR
Kemppainen et al 2008[439]	M/F	50	NR	NR	33.0	27.6	11.0	7.8	NR	NR
Ueno et al 2009[453]	M/F	58	NR[a]	NR	26.5	27.2	34.1	21.2	NR	NR
Barnes et al 2009[442]	M/F	42	95.6	82.9	36.1	30.1	24.6	18.3	NR	NR
Johansson et al 2009[427]	M	48	113.4	94.3	34.4	28.7	37.0	12.0	26.0	7.0
Hernandez et al 2009[444]	M/F	43	134.6	117.7	48.0	42.8	10.6	5.7	NR	NR

Table 4-8 cont'd

Trial	Sex	Age (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/hour)	AHI after intervention (events/hour)	ODI4 at baseline (episodes/hour)	ODI4 after intervention (episodes/hour)
Sleep AHEAD 2009[437]	M/F	61	102.9	90.5	36.8	33.0	22.9	17.5	18.6	13.1
Tuomilehto et al 2009[441]	M/F	50	101.2	90.5	33.4	29.9	10.0	6.0	NR	NR
Nerfeldt et al 2010[449]	M/F	52	122.0	110.0	40.0	35.0	43.0	28.0	42.0	23.0
Kline et al 2011[424]	M/F	46	105.6	104.9	35.3	35.0	32.2	24.6	24.5	21.5
Sengul et al 2011[440]	M	54	86.4	NR	29.7	29.2	15.1	11.0	NR	NR
Johansson et al 2011[445]	M	30-65	113.1	95.4	34.8	29.3	36.0	15.0	25.0	9.0

*NR= Not Reported

4.4.2 Effect of lifestyle intervention on obstructive sleep apnoea (OSA)

Figure 4-4 shows the forest plot of differences in AHI changes between intervention and control groups after intervention in 7 randomised controlled studies (n = 532). The pooled mean reduction in AHI was -6.04 events/hour (-11.18 to -0.90). Heterogeneity between studies was high (Q = 42.26, *df* = 6, p <0.00001, I^2=86%). Figure 4-5 shows forest plot of AHI changes after intervention from 9 before-and-after studies (n = 482). The pooled mean reduction in AHI was -12.26 events/hour (-18.51 to -6.02). Substantial heterogeneity was observed between studies (Q = 64.92, *df* = 8, p<0.00001, I^2 = 88%). All five uncontrolled studies with ODI4 outcome reported significant reduction in amount of oxygen desaturation after the intervention. Figure 4-6 shows forest plot of ODI4 changes after intervention in 5 uncontrolled studies (n = 236). The pooled mean reduction in ODI4 was -18.91 episodes/hour (-23.40 to -14.43). There was little heterogeneity between studies (Q = 4.23, *df* = 4, p = 0.38, I^2 = 5%).

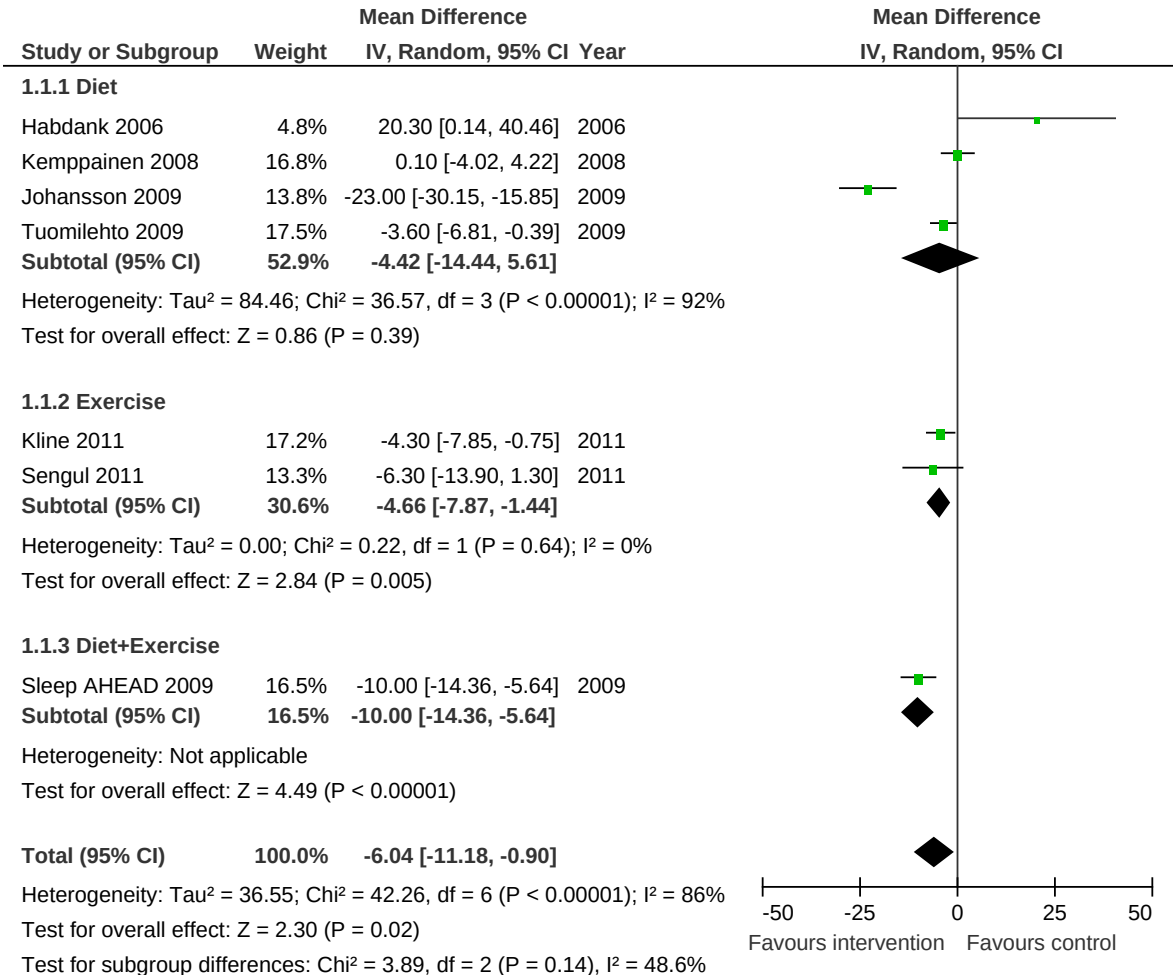

Figure 4-4. Forest plot of differences in AHI (events/hour) changes between intervention and control groups after intervention in randomised controlled studies. 95 CI indicates 95% confidence interval.

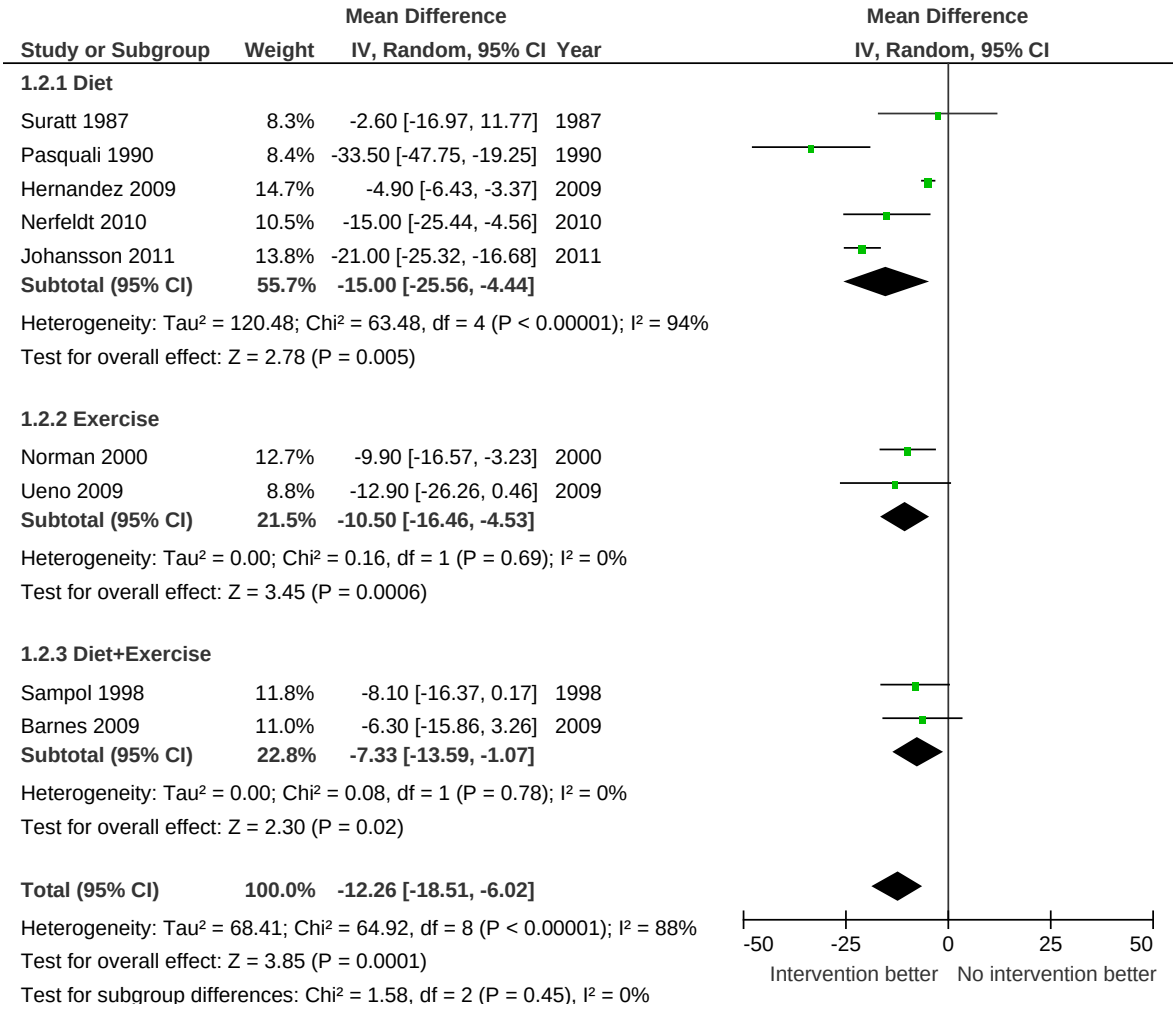

Figure 4-5. Forest plot of AHI (events/hour) changes after intervention in uncontrolled before-after studies 95 CI indicates 95% confidence intervals.

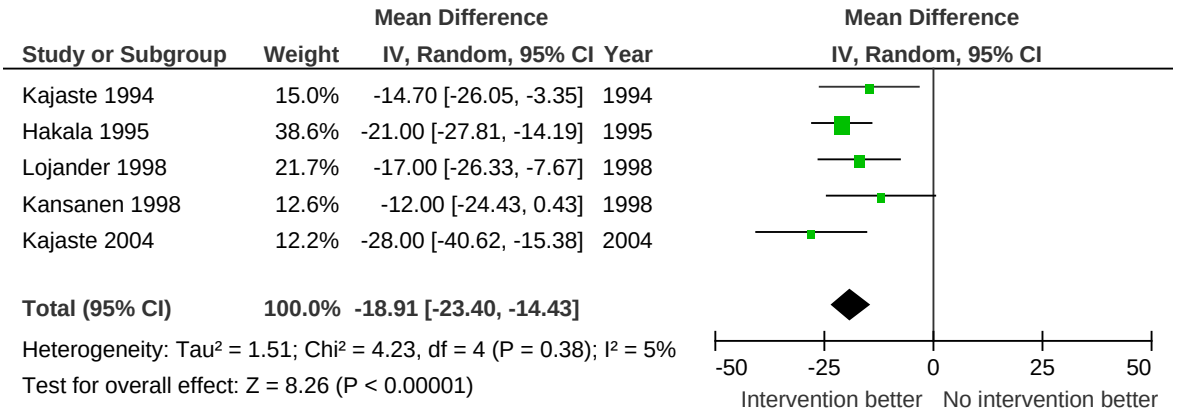

Figure 4-6. Forest plot of ODI4 (episodes/hour) changes after intervention in uncontrolled before-and-after studies. 95 CI indicates 95% confidence intervals.

4.4.3 Effect of lifestyle intervention on body mass index (BMI)

Figure 4-7 shows forest plot of differences in BMI changes between intervention and control groups after the intervention in randomised controlled studies. They reported a reduction in BMI after the interventions, but this was not statically significant. The pooled mean reduction in BMI was -2.32 kg/m^2 (-5.06 to 0.42) but heterogeneity between studies was very high (Q = 128.16, *df* = 5, p<0.0001, I^2 =96%). Figure 4-8 shows the forest plot of BMI changes after intervention in uncontrolled before-and-after studies. They also reported a significant reduction in BMI. The pooled mean reduction in BMI was -4.94 kg/m^2 (-5.66 to -4.21). No heterogeneity was observed within each type of lifestyle interventions (e.g. diet, exercise and both combined), but a significant reduction in BMI appeared to have been observed only in diet or combined interventions but not in exercise interventions (test for differences between subgroups, p = 0.003). From the data, diet and exercise together appear to be most effective, but there are too few studies (1 RCT and 2 before-and-after studies).

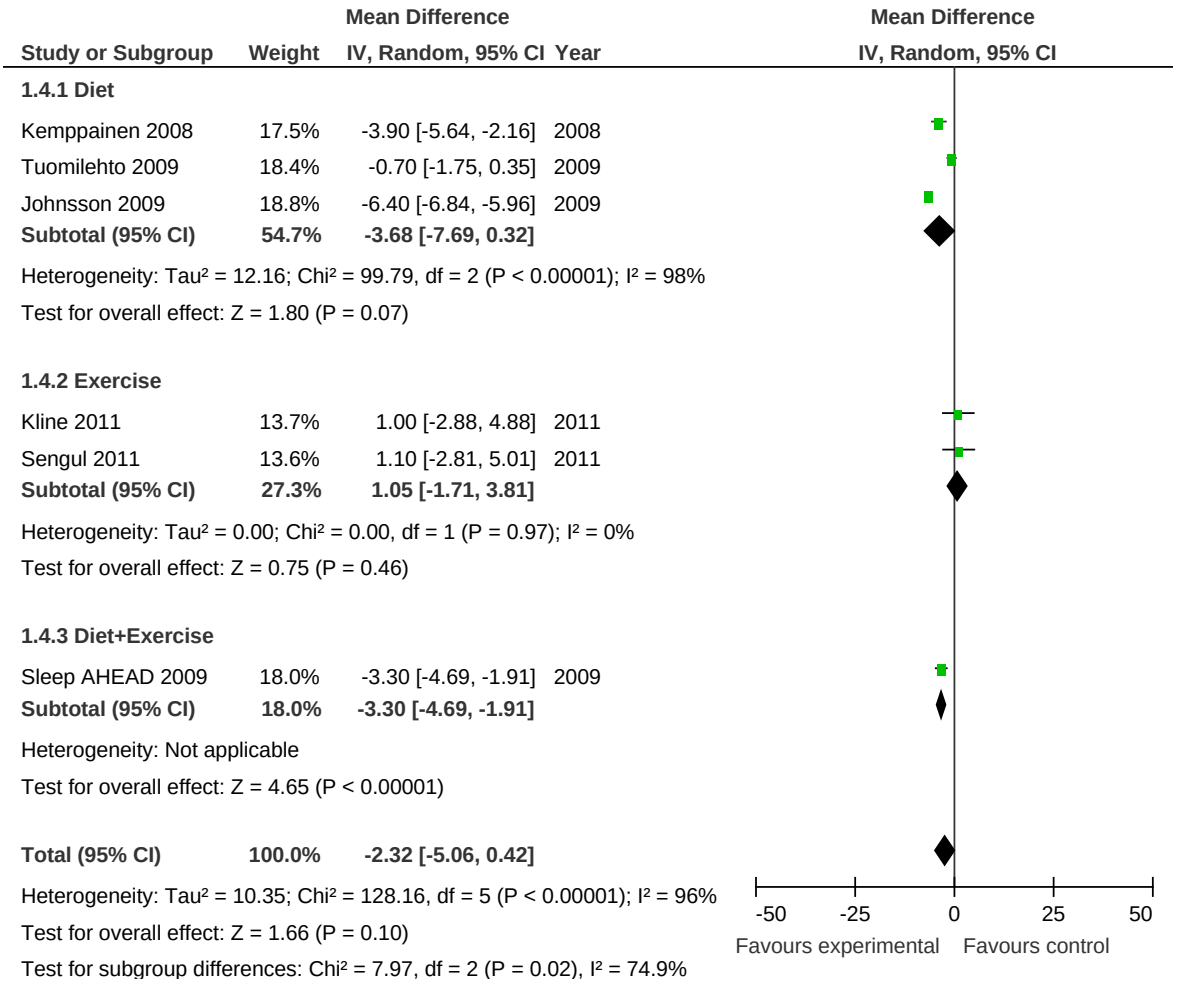

Figure 4-7. Forest plot of differences in BMI (kg/m^2) changes between intervention and control groups after intervention in randomised controlled studies. 95 CI indicate 95% confidence intervals.

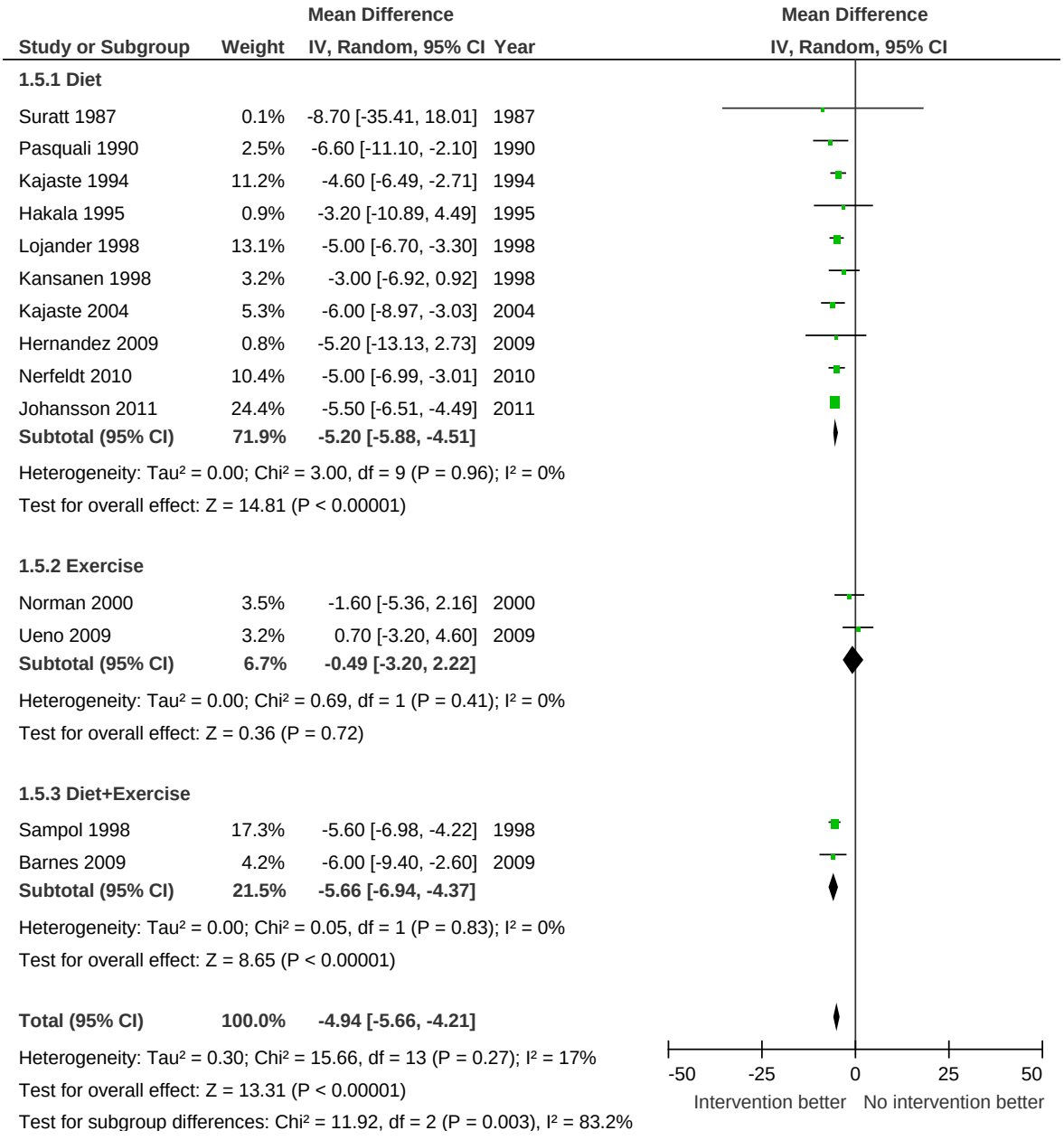

Figure 4-8. Forest plot of BMI (kg/m^2) changes after intervention in uncontrolled before-and-after studies. 95 CI indicates 95% confidence intervals.

4.4.4 Effect of lifestyle intervention on daytime sleepiness

Data on the effect of weight loss interventions on common OSA symptoms was markedly lacking across studies. For the meta-analysis, we presented the results from RCTs[427, 440, 441] first and then presented the results from before-after studies[442, 445, 449] as a subgroup.

Figure 4-9 shows the forest plot of differences in Epworth Sleepiness Scale (ESS) across RCTs and before-after studies. The pooled mean reduction of ESS from RCTs was -1.04 (-2.31 to 0.23) and no heterogeneity was found between studies (Q = 2.14, *df* = 2, p = 0.11, I^2 =0%). The pooled mean reduction of ESS from before-after studies was -2.87 (-4.30, -1.44) low level heterogeneity was found between studies (Q =3.16, *df* = 2, p = 0.21, I^2 =37%).

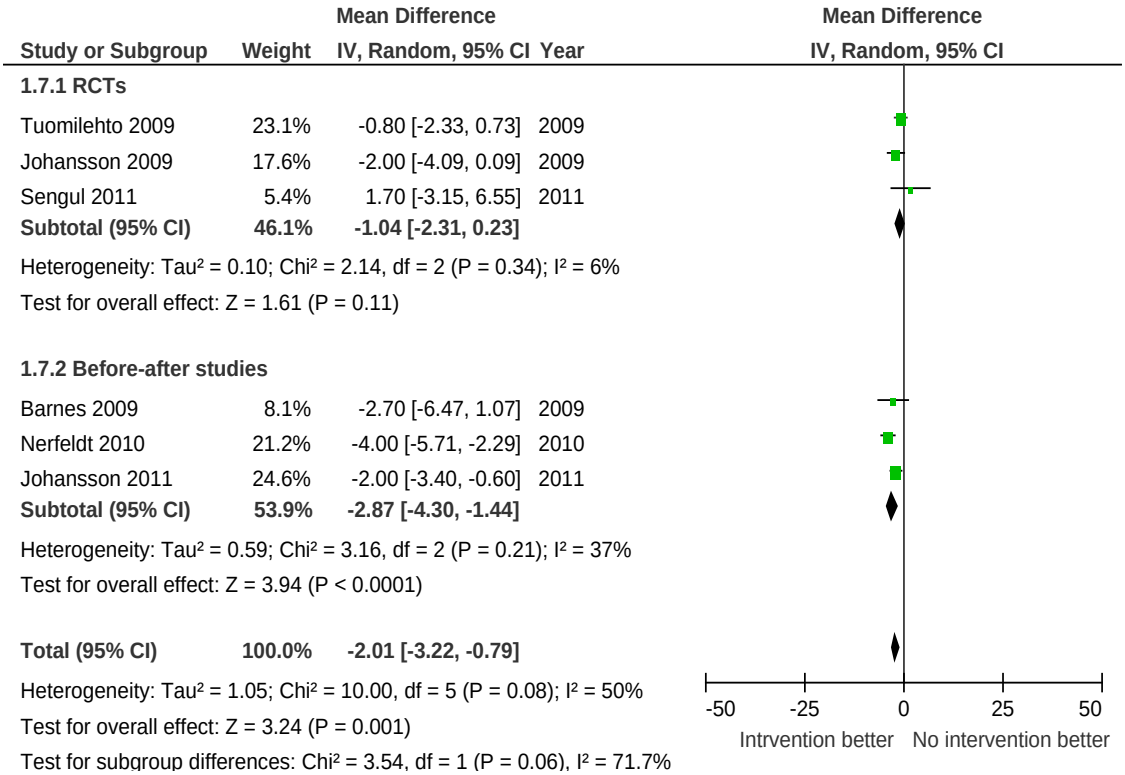

Figure 4-9. Forest plot of Epworth Sleepiness Scale (ESS) changes after intervention across the studies. 95 CI indicates 95% confidence intervals.

4.4.5 Sensitivity analysis and investigation of heterogeneity

We re-ran the meta-analysis excluding studies judged to be of lower quality. The overall findings remained unchanged in the sensitivity analysis.

Substantial heterogeneity was observed between studies in the meta-analyses of AHI and BMI. I explored the source of heterogeneity by performing subgroup analyses and stratified the studies according to the baseline level of AHI (>25, 15-25, <15 events/hour), change in BMI (0-3, 3-5, ≥5 kg/m^2), and duration of intervention (≤12, >12 weeks) (Table 4-9). The results indicate that the greatest source of heterogeneity was from studies with higher AHI at the baseline, and also those with greater change in the BMI. Meta-regression of the studies suggested a positive correlation between baseline AHI and change in AHI (r = -0.41, p = 0.001) (Figure 4-10) and between weight loss and change in AHI (r = 0.56, p = 0.186) although the latter did not reach statistical significance partly due to the small number of studies (Figure 4-11).

Table 4-9. Investigation of heterogeneity and findings from subgroup analysis.

Subgroup category	No. of studies	Pooled mean change in AHI, 95% CI	Heterogeneity (I^2)
Randomised Controlled Studies			
Baseline AHI			
AHI≥ 25 (events/hour)	3	-4.91 (-21.97, 12.15)	93%
AHI 15-25 (events/hour)	2	-9.08 (-12.87, -5.30)	0%
AHI<15 (events/hour)	2	-1.99 (-5.58, 1.61)	48%
Test for subgroup differences: (p = 0.03)			
Change in BMI			
0-3 kg/m^2	2	-7.12 (-9.14, -5.10)	12%
3-5 kg/m^2	2	-4.11 (-5.89, -2.33)	0%
≥5 kg/m^2	2	-13.74 (-35.10, 7.61)	95%
Test for subgroup differences: (p = 0.07)			
Duration of intervention			
≤12 weeks	4	-8.78 (-15.65, -1.87)	88%
>12 weeks	3	-0.67 (-11.18, 9.83)	88%
Test for subgroup differences: (p = 0.52)			
Uncontrolled before-after studies			
Baseline AHI			
AHI≥ 25 (events/hour)	6	-15.60 (-22.95, -8.24)	71%
AHI 15-25 (events/hour)	2	-8.72 (-14.19, -3.25)	0%
AHI<15 (events/hour)	1	-4.90 (-6.43, -3.37)	N/A[a]
Test for subgroup differences: (p = 0.01)			
Change in BMI			
0-3 kg/m^2	2	-10.50 (-16.46, -4.53)	0%
3-5 kg/m^2	1	-15.00 (-25.44, -4.56)	N/A[a]
≥5 kg/m^2	6	-12.30 (-20.92, -3.68)	92%
Test for subgroup differences: (p = 0.76)			
Duration of intervention			
≤ 12 weeks	3	-14.79 (-24.41, -5.17)	69%
>12 weeks	5	-12.66 (-19.85, -5.47)	76%
Test for subgroup differences: (p = 0.52)			

*N/A= Not Applicable

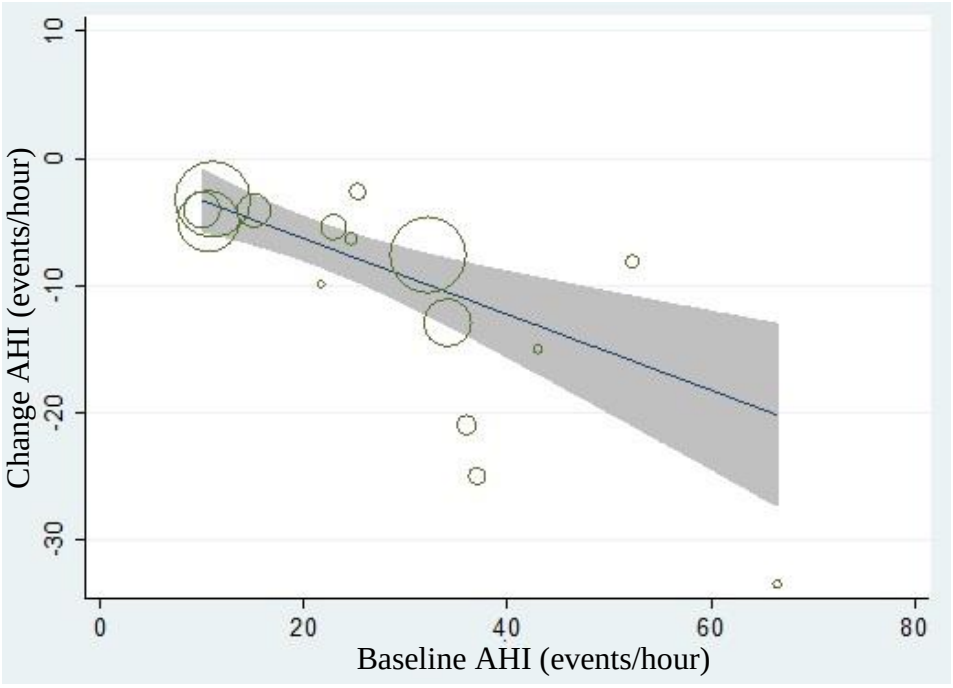

Figure 4-10. Regression analysis of pooled data on correlation of baseline AHI and change in AHI (the shading area represent the 95% confidence interval).

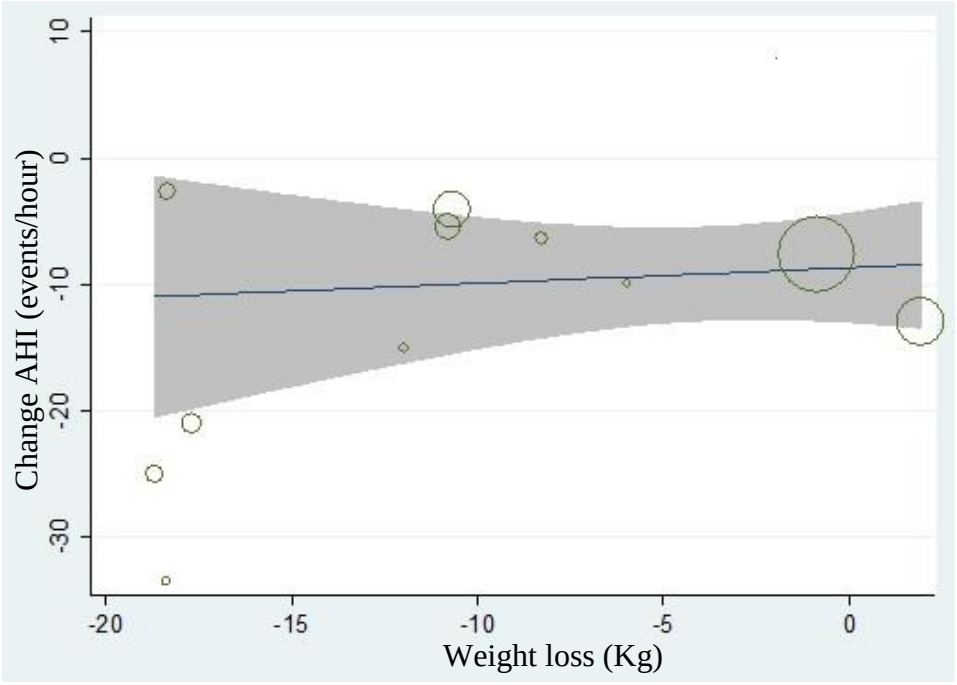

Figure 4-11. Regression analysis of pooled data on reduction of weight and change in AHI (the shading area represent the 95% confidence interval).

4.4.6 Analysis of publication bias

I assessed the presence of potential publication bias using Dear and Begg's test.[435] There was no evidence of publication bias across 21 studies (Figure 4-12). I computed a simulation-based *p*-value to assess the null hypothesis of no selection bias across studies and the overall computed p-value was 0.76, which strongly support the previous indication. The estimated weight function which is a proportional to the probability that a study is published introduced by Dear and Begg,[435] showed random configuration (no observable trend), which visually confirmed the lack of bias across the studies. Using Dear and Begg[435] the estimated weight function for the current study was as follows: 0.330, 0.088, 0.359, 0.999, 0.179, 0.385, 0.174, 0.194, 0.153, 0.999, and 0.195. The weight was constructed based on the two sided *p*-value. For the (n) independent studies then the number of point in the weight function was equal to 1 + integer (n/2).

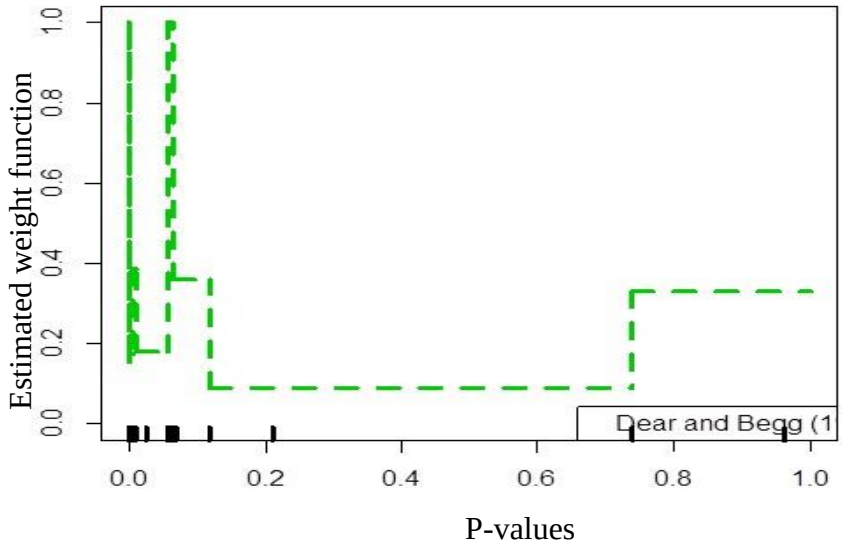

Figure 4-12. Estimated of publication bias based on the Dear and Begg's test.[435]

4.5 Discussion

CPAP is commonly employed for the treatment for OSA and its sequelae. However, the adherence to CPAP is usually below the optimal level.[172] The non-adherence level (≤4 hours of use per night) ranges from 29% to 83% among OSA patients.[456] For the majority of patients with OSA, lifestyle change and weight loss are recommended by guidelines,[174] but supportive evidence for this recommendation remains unexamined through systematic review and meta-analysis. This study provides a systematic review of the literature and quantitative assessments of the effect of the non-surgical and non-pharmaceutical weight loss interventions on OSA. Based on the 21 studies (both RCTs and uncontrolled before-after studies) included representing 893 patients with OSA, a reduction in AHI was detected after completion of the intervention. The effect of the interventions seemed larger in uncontrolled before-after studies than in controlled studies. A significant portion of this can be explained through methodological differences between study designs. In before and after studies, both participants and investigators are aware that they are receiving active treatment, which will influence outcomes. It is well accepted that the most vigorous approach for detecting a cause-effect association between treatment and outcome is using a randomised controlled trial approach. In clinical trial design, investigators seek to fully control the exposure in terms of its type, amount, and duration, and most importantly who receives it through the randomisation procedure. A control group is the main feature of all randomised controlled trials. The main purpose of the control group is to measure cumulative effects of all other factors (spontaneous improvements, non-specific responses, and specific treatment effects) other than active treatment itself that can influence outcome over time. In absence of control arms in uncontrolled before-after studies, participants may change their behaviour as a result of simply being observed

by a healthcare worker rather than because of any manipulation of independent variables (e.g. the Hawthorne effect). However, even in clinical trials the Hawthorne effect may blunt the difference between the placebo and the active treatment, but cannot explain the absence of a significant difference. Concealed random allocation is another important feature of randomised controlled trials that eliminates (or at least greatly reduces) confounding from known and unknown prognostic factors, thus the groups become equivalent in terms of their prognosis at baseline). Through the process of concealment, unpredictability is assured, which crucial in preventing selection bias. Blinding is another feature of randomised controlled trials that ensures that views of clinicians and statisticians cannot bias the outcomes, so that outcomes are measured with the same degree of accuracy and completeness in every participant. Blinding prevents measurement bias as opposed to concealed random allocation which prevent selection bias and confounding bias. Finally, in randomised controlled trials, patients are analysed within the group that they were initially allocated regardless of whether they experienced the intended intervention (intention to treat analysis).

This allows the findings to be more applicable to the clinical setting. I explored the source of heterogeneity by performing sub-group analysis; I categorised the studies into three groups based on their baseline AHI, duration of intervention, and change in BMI.

4.5.1 Obesity is an important risk factor for OSA

It is known that obesity is an important risk factor for OSA.[161] The increasing prevalence of OSA, driven by increasing levels of obesity necessitates an approach to treatment that not only addresses the symptoms of OSA, but also the obesity that contributes to some extent to OSA development and severity.

Obesity is associated with a higher risk of OSA, but conversely OSA is found to be associated with an increased risk for obesity.[167] The mechanism for these associations are complex with many factors contributing to the relationship between obesity and OSA. These include anatomical narrowing of the upper airway and physiological alterations in airway control. Additionally, obesity impacts on ventilation through increased abdominal pressure secondary to visceral adiposity accompanied by impaired diaphragmatic and ribcage movement. Other mechanisms are described above. On the other hand, OSA may promote obesity.[167] Sleep fragmentation as a result of OSA makes individuals sleepy during the day, which could ultimately lead to inactivity. [457] Evidence indicates that OSA could also negatively influence glucose metabolism.[458] For example, growth hormone (GH), a hormone that regulates metabolism is secreted during slow-wave sleep. It is believed that the negative effect of OSA on slow-wave sleep, and hence GH, may be a potential explanation on how OSA causes diabetes.[458] The negative impact of sleep disturbance on appetite and energy metabolism could be another explanation on how OSA could promote obesity.[459] It can be hypothesised that OSA could alter the secretion and responsiveness of appetite hormones such as leptin and ghrelin, but one study has suggested that this may not be the case.[460]

4.5.2 Effect of lifestyle interventions on OSA

The meta-analysis of the seven randomised controlled trials detected a reduction in AHI after completion of the intervention. The meta-analysis of fourteen uncontrolled before-and-after studies also showed a reduction in AHI and ODI4. Substantial heterogeneity was observed across studies that reported AHI as an outcome. Subgroup analysis showed that heterogeneity resulted from the studies with severe OSA at baseline with meta-regression indicating a linear relationship between baseline AHI

and reduction in AHI, while the latter suggests a greater intervention effect in patients with more severe OSA, the possible influence of regression to the mean, can be ruled out,[461] which is a statistical feature that can be caused by enrolment of participants in trials based on a single baseline measurement. Regression to the mean is a main issue within uncontrolled before-after studies. However, in RCTs, the effect should be equal between groups and therefore its influence is expected to be cancelled out in 'between-group difference' data.

Overall, few studies demonstrated the normalisation of AHI with the interventions employed. For the seven randomised controlled studies that have reported AHI as their outcome, only two studies[427, 437] attained a reduction in AHI of more than 10 events/hour and in nine uncontrolled studies that also reported AHI as their outcome, only three studies[445, 449, 451] reported a reduction in AHI of more than 10 events/hour. The significant reduction in ODI4 was achieved by all five uncontrolled studies. It seems that the interventions may have greater impact on reduction of ODI4 compared to AHI. Apart from OSA, obesity has effects on ventilation, which may explain the greater effect observed with ODI4. The results indicated that interventions that employed physical activity alone were not successful in reducing AHI compared to dietary approaches. A combination of diet and physical activity, however, resulted in significant reductions in AHI. While physical activity alone may not be as effective for weight loss as dietary interventions, it has a role in weight loss maintenance.[424]

The exact mechanism underlying the effect of lifestyle intervention on OSA is yet to be confirmed, because, at least in the meta-analysis of RCTs, there was no significant difference in BMI. The results from the studies with physical activity weight loss showed no significant change in body weight and BMI, yet a positive effect on AHI.

Interestingly, a recent published meta-analysis[426] on the effect of weight loss via bariatric surgery reported that the mean AHI still remained at moderate levels even after surgical weight loss. It might indicate that improvement in OSA might go beyond the weight loss.[462] There are several hypotheses regarding the impact of increased physical activity and reduced AHI.[268, 370, 462] It has been previously suggested that thermogenic enhancement, and energy alterations effectively contribute to changes in sleep-awake cycle.[463] It has been found that exercise training normalises chemoreceptor sensitivity in athletes which can improve breathing.[464] It is also hypothesised that a further possible cause of decrease in AHI is increased strength of tongue muscles as a result of inspiratory and expiratory pressure following increased physical activity.[465]

4.5.3 Effect of lifestyle interventions on BMI

The pooled estimate of six randomised controlled trial (one trial[438] did not report the data on change of BMI) showed a decrease in BMI, but this was not statically significant. The meta-analysis of fourteen uncontrolled before-after studies showed a significant reduction in BMI. I observed relatively mild heterogeneity across studies, therefore sub-group analysis was performed and the results showed that the main source of the heterogeneity comes from greater changes in BMI $\geq$5 kg/m^2.

Three RCTs[427, 437, 441] that investigated the impact of weight loss on severity of OSA have reported that a mean range of weight loss by 10-16% can reduce AHI by 20% to 50%. Three uncontrolled before-after studies[442, 449, 451] on weight loss also reported that the average weight reduction by 13% and 30% is associated with a decrease in AHI by 10% to 50%. A prospective analysis from the Wisconsin Sleep Cohort[161] demonstrated that a 10% weight loss was associated with a 26% reduction in AHI. However it seems

less likely that the 10% reduction of weight from baseline could be applicable to all the individuals as there could be other factors that contribute to the reduction of AHI. Johansson and colleagues[427] suggested that the baseline AHI is a strong predictor for reduction in AHI using a dietary weight loss intervention. They indicated that patients with severe OSA at baseline are more likely to benefit from the intervention.[427] Foster and colleagues[437] in the Sleep AHEAD study also reported that the initial AHI and weight loss contributes to the change in AHI. They reported that a 1-kilogram decrease in total body weight was associated with a reduction in AHI of 0.6 events/hour.[437] An uncontrolled before-after study by Hernandez and colleagues[444] also postulated that patients with severe OSA had a greater reduction in AHI. The amount of weight loss that an individual with OSA needs to achieve a significant reduction in AHI is unique.[451] The confounding part is otorhinolaryngological anatomy differences between individuals.[466, 467] The adipose tissue distribution is different for different individuals, which makes it difficult follow a single recommendation for weight loss in order to achieve OSA improvement.[468]

A major obstacle with lifestyle weight loss interventions the sustainability of reduced weight and adherence to the new lifestyle. Data describing a longer follow-up period is extensively lacking. Tuomilehto and colleagues[441] indicated that after a one year follow-up, the average weight loss of their participants was 11 kg. Kajaste and colleagues[433] also indicated that at 6-month follow-up, the mean reduction of weight loss was 19 kg and at 2-year follow-up was 13 kg which demonstrated that the participants were enthusiastic to sustain to the changes. The result of the 2-year dietary weight loss intervention by Nerfeldt and colleagues[449] indicated that sustained improvement in OSA severity was acquired following long-term weight loss maintenance. Similar improvements were obtained following a 1-year weight loss

program by Johansson and colleagues.[427] The Sleep AHEAD study[469] examined whether the initial improvement in OSA using intensive lifestyle intervention would be maintained after a 4-year follow-up duration. The results demonstrated that amount of weight loss over time was a strong predictor of change in AHI. Despite a 50% weight regain, however, improvement in AHI persisted at four years.

Using anti-obesity medication could potentially be considered as a promising approach to achieve weight loss maintenance in long term.[470-472] Thus, more long-term studies are required to examine the effectiveness of such treatment in sleep apnoea improvement.

4.5.4 Effect of lifestyle interventions on daytime sleepiness

Daytime sleepiness is a well-recognised symptom of OSA. Daytime sleepiness is associated with an increased risk of road and occupational accidents. Data on the impact of lifestyle weight loss intervention on daytime sleepiness are broadly lacking and surprisingly only few studies, three randomised controlled trials[427, 440, 441] and three before-after studies[442, 445, 449], examined the impact of lifestyle intervention on excessive daytime sleepiness or other symptoms of OSA. All of these studies had measured the daytime sleepiness via the Epworth Sleepiness Scale (ESS) which is a validated self-administrated questionnaire that evaluates the likelihood of dozing off in 8 different situations.[31] The higher total scores indicate higher levels of sleepiness.[31] The results indicate that lifestyle weight loss intervention could improve the ESS score. It should be taken into account that although the OSA patients subjectively reported better ESS, it does not indicate that objective measures of sleepiness are necessarily consistent with these results.[473] Future studies are needed to measure sleepiness via objective measures such as the Multiple Sleep Latency Test (MSLT) or

the Multiple Wakefulness Test (MWT). Obese individuals are more likely to feel sleepy and this can be independent of OSA.[168] Even following the completion of the lifestyle intervention, the majority of the patients were still in the obesity category range (BMI ≥30 kg/m^2). The adverse consequences of untreated excessive daytime sleepiness should be recognised. Evidence indicates that a reduction in weight via bariatric surgery did not eliminate the OSA symptoms and in particular daytime sleepiness.[173] Weight loss may not be considered as an effective therapy method for OSA, however even minimal weight loss has been found to be associated with a reduction in metabolic parameters.[474] For example, in a recent 4-arm RCT,[475] 439 obese middle aged women were assigned to dietary weight loss, exercise, both diet and exercise intervention or control group. The success of the interventions was defined as 10% weight loss from baseline. Following completion of 12 months interventions, a significant improvement was detected in insulin resistance measured by the Homeostasic Model of Assessment-Insulin Resistance (HOMA-IR) in the diet (-24%, $p<0.001$) and both diet and exercise (-26%, $p<0.001$) groups compared with the control group. Moreover, individuals with impaired fasting glucose (5.6-6.9 mmol/L) in the diet (OR 2.5, 95% CI 0.8 - 8.4), exercise (OR 2.76, 95% CI 0.8 - 10.0), both diet and exercise (OR 3.1, 95% CI 1.0 - 9.9) were more likely to regress to normal fasting glucose compared with controls.[475]

4.5.5 Clinical implications

Compared to bariatric surgery, lifestyle weight loss interventions such as diet and physical activity with lower cost and lower adverse outcomes are a potential treatment option for OSA improvement. These interventions, however, based on the current evidence examined, are unlikely to normalise breathing during sleep. Nevertheless, a sufficient change in AHI is likely to reduce the severity of OSA, which could, in turn, reduce its cardiovascular consequences.[476] The meta-regression carried out, although not statistically significant, most likely due to lack of statistical power, shows that the greatest weight loss is associated with greatest improvement in AHI. It appears that at least a 5% and preferably at 10% weight loss is required to be beneficial to making the greatest impact on OSA parameters and cardiovascular health.[427] Importantly, those with greatest AHI at baseline, who are at greatest risk for the cardiovascular consequences of OSA, are most likely to benefit from the lifestyle interventions employed.

The most dramatic weight loss has been observed with bariatric surgery and interventions employing VLCD (intake <800 $kcal \cdot d^{-1}$).[173, 477, 478] A systematic review of randomised weight loss trials with a minimum follow-up of a year suggested that VLCD achieved up to 10% weight reduction from baseline after a year, compared with pharmacologic treatment (8% weight reduction).[479] The long-term outcomes of bariatric surgery and VLCD interventions are unclear with both being associated with varying degrees of weight regain and potentially the resurgence of OSA.[480] The findings from studies employing VLCDs, however, demonstrate that this approach may be useful clinically for reducing measures of OSA.

Based on my findings, lifestyle weight loss interventions cannot be accepted as a curative treatment for OSA. As stated earlier, OSA is associated with an increased risk of metabolic disturbances[481] and even a slight change in weight may help to reduce these metabolic abnormalities. It is well-known that weight reduction as a treatment for normalisation of sleep among OSA patients is certainly more difficult than weight loss maintenance among these individuals. Lifestyle weight loss interventions can be used in the early stage of the disease. A recent published study by Hood and colleagues[482] postulated that weight loss via lifestyle intervention could potentially increase CPAP adherence.

4.5.6 Strengths and limitations

I conducted a comprehensive systematic review and meta-analysis to evaluate the effectiveness of lifestyle weight loss intervention for OSA patients. One of the strengths of the study is a published protocol which indicates that the research strategy and inclusion criteria have been checked by peer review. [429] As a result of the small number of randomised controlled trials identified, uncontrolled before-and-after studies were also included in this review to provide supportive evidence. Two independent reviewers searched the relevant studies and also checked data extraction and data analysis procedures. A recent published systematic review and meta-analysis[483] including 9 studies representing 557 OSA patients, evaluated the efficacy of dietary weight loss interventions. The results demonstrated that the severity of OSA was noticeably improved by such interventions. The study combined the results of both RCTs and uncontrolled before-after studies. Uncontrolled before-and-after studies, however, have limitations. These include small sample size, lack of control group, and systematic errors. Additionally, I evaluated the impact of physical activity

interventions on OSA. I statistically assessed the effect of potential selection bias across the studies and computed the overall p-value and the results showed that the study is free from publication bias. The overall quality of the included studies was assessed via Cochrane risk of bias tools and Cochrane Effective Practice and Organisation of Care Group (EPOC) risk of bias tool. The study also benefited from compliance of PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). A potential source of heterogeneity was explored. Appropriate subgroup analysis was planned to investigate the source of heterogeneity when required.

A potential limitation of the study is that the overall quality of included randomised studies was fairly poor. The absence of control groups and low sample size of before-after studies makes it difficult to draw any concrete conclusions from these studies. The mean age of the participant across the studies is 45 years and above, so the results cannot be generalised to younger individuals.

4.6 Key points

The results of the study revealed that lifestyle weight loss interventions could potentially improve OSA. It should be taken into account that such interventions are insufficient to normalise breathing during sleep, but may be used to increase the efficacy and adherence of other treatments such as CPAP. Future robust randomised controlled trials with longer follow-up periods are needed to confirm the results. The improvement in OSA by utilisation of such interventions may go beyond weight loss, and future studies are needed to control for potential mediators such as upper airway size, nasal resistance, and lung volume. To date, several treatment options have reported residual sleepiness despite the reduction of AHI up to the normal level (<5 events/hour). The adverse outcome of excessive daytime sleepiness needs to be more appreciated in future studies.

5 CONCLUSIONS AND FUTURE WORK

5.1 Predictors of total sleep duration in older Chinese adults- The Guangzhou Biobank Cohort Study (GBCS)

The findings indicated that being female, older, widowed, having lower education level, and having lower income levels, were strongly associated with short sleep duration, while hypertension was strongly associated with long sleep duration. Additionally, the results of the logistic regression model controlling for age, gender, marital status, education level, income level, smoking, alcohol consumption, physical activity, obesity, hypertension and diabetes showed that long sleep duration was significantly associated with obesity and both short and long sleep duration were associated with hypertension in the whole sample. No significant association was found between sleep duration and diabetes in the whole sample. The results of the stratified analysis by gender and age showed that there was an inverse association between short and long sleep duration and obesity among males aged 65 years and older. In females, aged below 65 years, only long sleep duration was positively associated with obesity. Short sleep duration was associated with hypertension among older males, while in younger females, long sleep duration was associated with increased risk of hypertension. Moreover, in older females, only short sleep duration was positively associated with increased risk of diabetes.

Effect of sleep duration on body weight among younger populations is well known; however, the presence of such an association among older populations is less studied and requires further investigation. Alteration in sleep patterns in older populations may not have a similar effect on metabolism as in younger individuals, due to the high prevalence of other chronic conditions such as hypertension, diabetes, and arthritis, which may influence their sleep. The present study also suggested that the association

between sleep duration, obesity, hypertension and diabetes may differ between men and women. Present knowledge of the mechanisms for such associations is insufficient to explain sex differences. Thus, findings of the study on this particular issue should be confirmed in future studies. A better understanding of the lifestyle factors that correlate with sleep duration will provide perspectives for future studies to establish appropriate therapies and health interventions to improve sleep behaviours in order to enhance health and functioning among older populations.

5.1.1 Future work

The present study was one of the few studies that have examined factors associated with sleep duration among a representative sample of older individuals and also examined the association between sleep duration and obesity, hypertension, and diabetes among men and women. Identifying determinants of sleep duration is important because such factors can be addressed in future health promotion interventions aiming to increase sleep duration among potentially sleep-deprived individuals. Sleep problems could be potentially improved by targeting modifiable lifestyle factors such as diet, smoking, drinking, and physical activity, which may also help prevent the initiation and progression of chronic diseases. The association between sleep duration and health complications should be further examined in older individuals, as sleep patterns change dramatically across the life span. The potential gender differences in the relationship between sleep duration and obesity, hypertension and diabetes require further investigation, since evidence from previous literature is relatively controversial. Future studies should be conducted to investigate the hormonal difference in response to sleep duration in men and women.

The present study and also the majority of population-based studies and surveys have employed self-report measures of sleep duration, which could not necessarily indicates actual sleep time and may reflect the total time in bed. Nevertheless, time in bed, the usual surrogate for sleep in large population studies, has been shown to have implications for health. With increasing availability and reduced costs of actigraphy, it will be possible to include an objective measure of sleep in population studies. Future studies should aim to sufficiently characterise "short sleepers" and "long sleepers", and ascertain that from what extent deviation from certain actual sleep time or the total time sleeping in bed should be referred to as short sleep or long sleep. Future studies should also control for a greater range of potential cofounding factors.

5.2 The complex associations among sleep quality, anxiety-depression, and quality of life in patients with extreme obesity

The above published study was the first study to investigate the associations among poor sleep quality, and mood and quality of life, in individuals with extreme obesity. The study benefited from a large clinical sample size and detailed statistical analysis. Overall, the participants reported short sleep duration and poor sleep quality. Anxiety and depressive symptoms were relatively high among these individuals. Moreover, participants reported low scores on all components of quality of life, and in particular self-esteem. The findings from linear regression analysis showed that poor sleep quality and excessive daytime sleepiness were positively associated with anxiety and depression symptoms and these were also associated with impaired quality of life. Structural equation modelling (SEM) supported the earlier findings from regression models. Short sleep duration and poor sleep quality are relatively prevalent among obese individuals. It is well known that insufficient sleep per se may contribute to incident and progression of obesity. Addressing sleep problems among obese

individuals could potentially prevent worsening obesity and progression of further psychological conditions among these individuals.

5.2.1 Future work

Previous studies among samples of non-obese individuals showed that there is a close relationship between sleep loss and depression that may also have deleterious impact on individuals' quality of life. Previous studies have consistently reported a high prevalence of psychiatric disorders among those with insomnia and vice versa. Prior work has also shown that for individuals who suffer from both conditions, treating insomnia may eliminate depressive symptoms. It is known that poor sleep quality is prevalent among individuals with extreme obesity, and poor sleep may increase the risk of development of further adverse physical and mental health outcomes and also worsen obesity per se. It can be hypothesised that treatment of sleep problems among individuals with extreme obesity could potentially prevent worsening obesity, and could also prevent initiation and progression of psychological conditions such as depression among these individuals. Future randomised controlled trials are needed to investigate the effectiveness of sleep improvement interventions on body weight, mood, and quality of life.

Future experimental studies are needed to examine the underling mechanisms between sleep loss and mental health. Additional investigation needs to be conducted to fully explore the potential role neurobiological consequences of sleep loss on initiation and development of depression. Further functional imaging techniques are needed to fully assess the patterns of activity in specific brain regions that are both implicated in sleep and in depression.

5.3 The effectiveness of lifestyle interventions on obstructive sleep apnoea (OSA): systematic review and meta-analysis

Given the increase in prevalence of obesity, OSA is likely to become an even greater health challenge. My published study provided a systematic review of the literature and quantitative assessments of the effect of the non-surgical and non-pharmaceutical interventions on OSA. Twenty-one studies, representative of 893 patients with OSA, were found to be eligible for inclusion. The meta-analysis of seven randomised controlled trials involving 519 participants, detected a reduction in AHI after completion of the intervention. Additionally, the meta-analysis of fourteen uncontrolled before-and-after studies involving 374 participants showed a reduction in AHI and ODI4. The results also indicated that interventions that employed physical activity alone were not successful in reducing AHI compared to dietary approaches. A combination of diet and physical activity, however, resulted in significant reductions in AHI. Compared to bariatric surgery, lifestyle weight loss interventions such as diet and physical activity, which likely to be of lower cost with lower adverse outcomes, are a viable treatment option for OSA. These interventions, however, based on the current evidence examined, are unlikely to normalise breathing during sleep. Therefore, lifestyle weight loss interventions cannot be accepted as a curative treatment for sleep apnoea. However, lifestyle interventions have additional health benefits that could improve the quality of life in patients with OSA.

5.3.1 Future work

Excessive daytime sleepiness is a well-recognised symptom of OSA that may increase the risk for several adverse health conditions. Data on the impact of lifestyle weight loss on daytime sleepiness intervention are broadly lacking. Future studies are needed to measure sleepiness via objective measures such as the Multiple Sleep Latency Test

(MSLT). None of the studies examined investigated the impact of lifestyle interventions in OSA patients on quality of life. Also, no health economic evaluation has been carried out to examine whether these interventions are cost-effective. Future randomised controlled trials need to incorporate these essential components.

A major obstacle with lifestyle weight loss interventions is sustainability of the reduced weight and adherence to the new lifestyle. Data describing a longer follow-up period are extensively lacking. Additionally, the exact mechanism underlying the effect of weight loss on OSA is less well understood. There is a now need for larger randomised controlled trials aiming for at least a 10% weight loss and longer term follow-up to examine the effectiveness of such treatment scheme in improvements of sleep apnoea. In the meantime, given that there are cardio-metabolic benefits of weight loss, there is a need for a more proactive role in treating obesity amongst the OSA patient population.

5.4 Final conclusions

Sleep is one of the fundamental aspects of healthy living and increasing evidence suggests that it should be a pillar of a healthy lifestyle in addition to diet and physical activity. Insufficient sleep may have a deleterious impact on both physiological and psychological well-being. It should also be taken into account that impact of sleep on health could potentially be attenuated across the life span and is likely to be influenced by ethnicity and environmental factors. Untreated sleep disorders such as chronic sleep loss, excessive daytime sleepiness and OSA may result in road and occupational accidents and increase economic burden and health care utilisation. Overall, this thesis highlighted the potential link between different dimensions of sleep (sleep duration, sleep quality and obstructive sleep apnoea) and obesity. Moreover, it also suggested that the association between sleep duration and obesity may differ between older men and women. The evaluation of the sleep patterns among individuals with extreme obesity showed that these individuals have a short average sleep duration and reported poor sleep quality. The poor sleep factors were also shown to be associated with impaired mood and quality of life among these individuals. This may influence weight gain and influence weight loss outcomes, which needs to be confirmed through further study.

OSA often accompanies obesity. A slight reduction in severity of OSA may be achieved as a result of weight loss, using lifestyle interventions among obese individuals. Modification in lifestyle habits, including sleep behaviours, diet, and exercise maybe a key to maintaining a healthy weight. Although sleep problems contributes to obesity, the reverse association is also true, obesity may cause sleep problems. The nature and the direction of this association requires further study, using

measures from several domains, including sleep (objective and subjective), stress (physiologic, emotional, and social), and mental and physical health. In general, the obesity epidemic requires a multidimensional approach, promoting a healthy lifestyle, which includes attention to sleep quality and duration.

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Appendices

A) Informed consent form of the Guangzhou Biobank Cohort Study (*Chapter 2)*

B) Questionnaires collected as part of routine data collection in Weight Management Service (*Chapter 3*)

Appendix 1b: Pittsburgh Sleep Quality Index (PSQI)

Appendix 2b: Epworth Sleepiness Scale (ESS)

Appendix 3b: Hospital Anxiety and Depression Scale (HADS)

Appendix 4b: Impact of Weight on Quality of Life-Lite (IWQOL-Lite)

C) Standard lung volume as measured with a spirometer (*Chapter 4*)

D) Search strategy used to identify studies for systematic review (*Chapter 4)*

A) Informed consent form of the Guangzhou Biobank Cohort Study (*Chapter 2)*

Informed Consent Form

1) Completing a questionnaire which includes information about my diet, lifestyle and medical history.

2) Undertaking various physical examinations, including measurement of height, weight, hip and waist circumference, blood pressure, ECG, chest X-ray and lung function.

3) Providing a small sample of blood (about 15 ml), which will be stored and used for measurement of blood factors possibly related to various forms of chronic diseases (including biomarkers, genes, hereditary markers, genetic markers, cell culture), solely for the purpose of this study.

4) Monitoring my health status over the next 10-15 years or longer through local health clinics, hospitals or official disease registration systems.

- I understand that after the interview and physical examination, I will be given the results of various physical measurements, but as samples will not be assayed at present I will not be given any result for the blood assay. At a 1-year interval, I may be invited to participate again in the resurvey in order to assess the change of lifestyle and general health status.

- I understand that I am free not to participate in this study, and can withdraw at any time without needing to give a reason and without affecting my medical care.

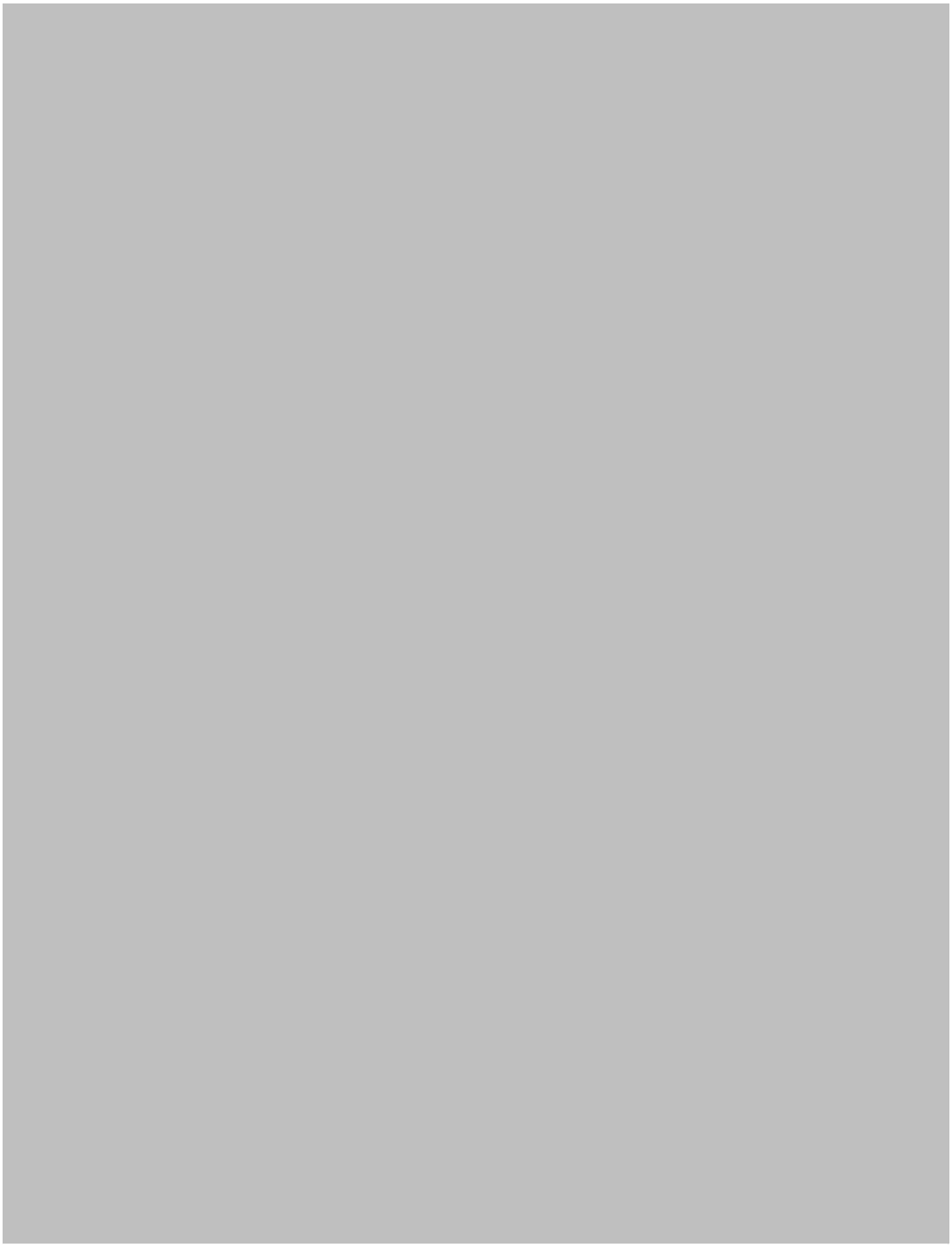
- I understand that all information provided by me will be treated confidentially, and that the research team that are responsible for the whole project will use the results to try to improve the prevention and treatment of common diseases, and that I shall not benefit financially from my participation.

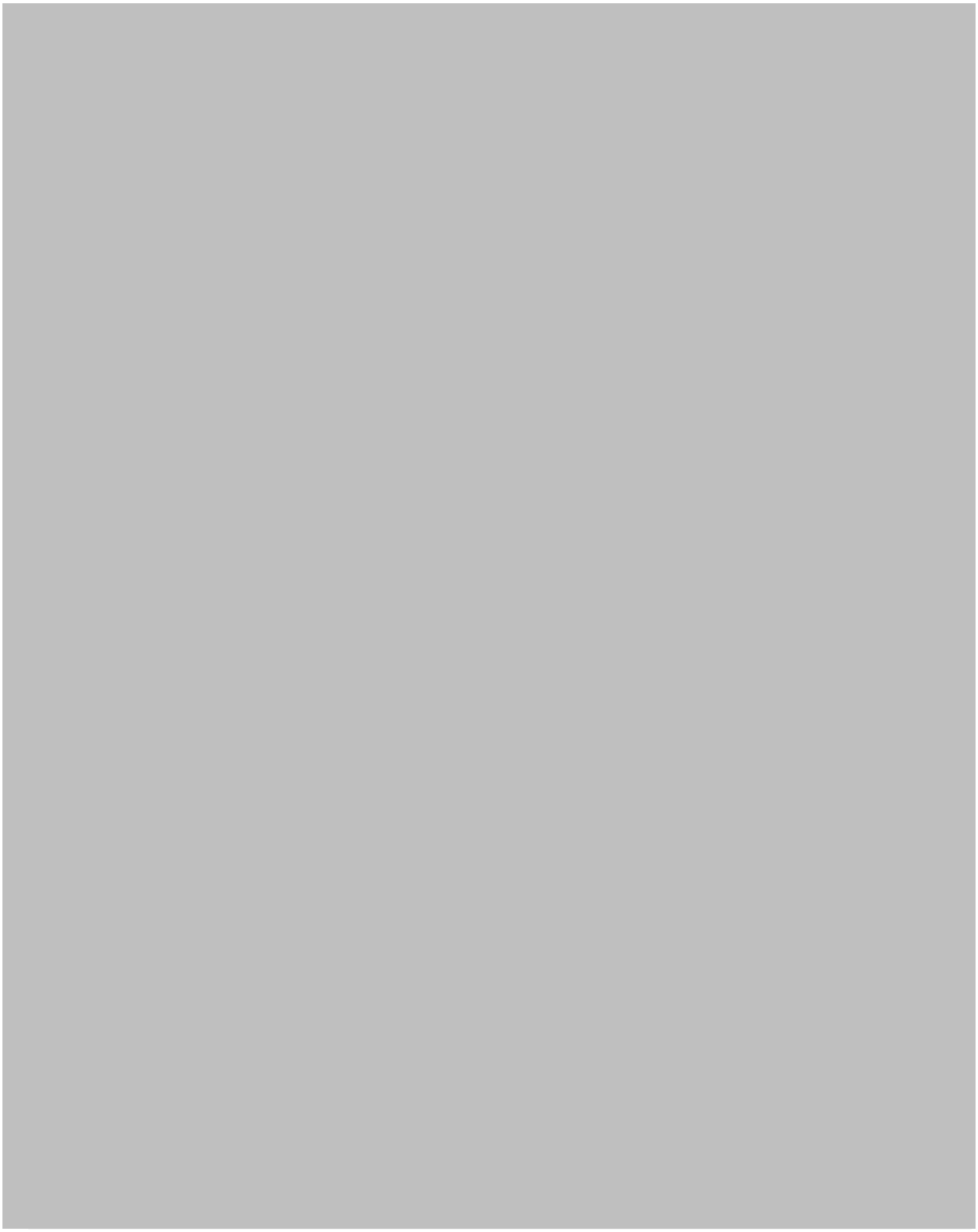
Signature: _____; Date: _____Year _____Month_____Day

Witness signature: _____; Date: _____Year _____Month_____Day

Appendix 1b

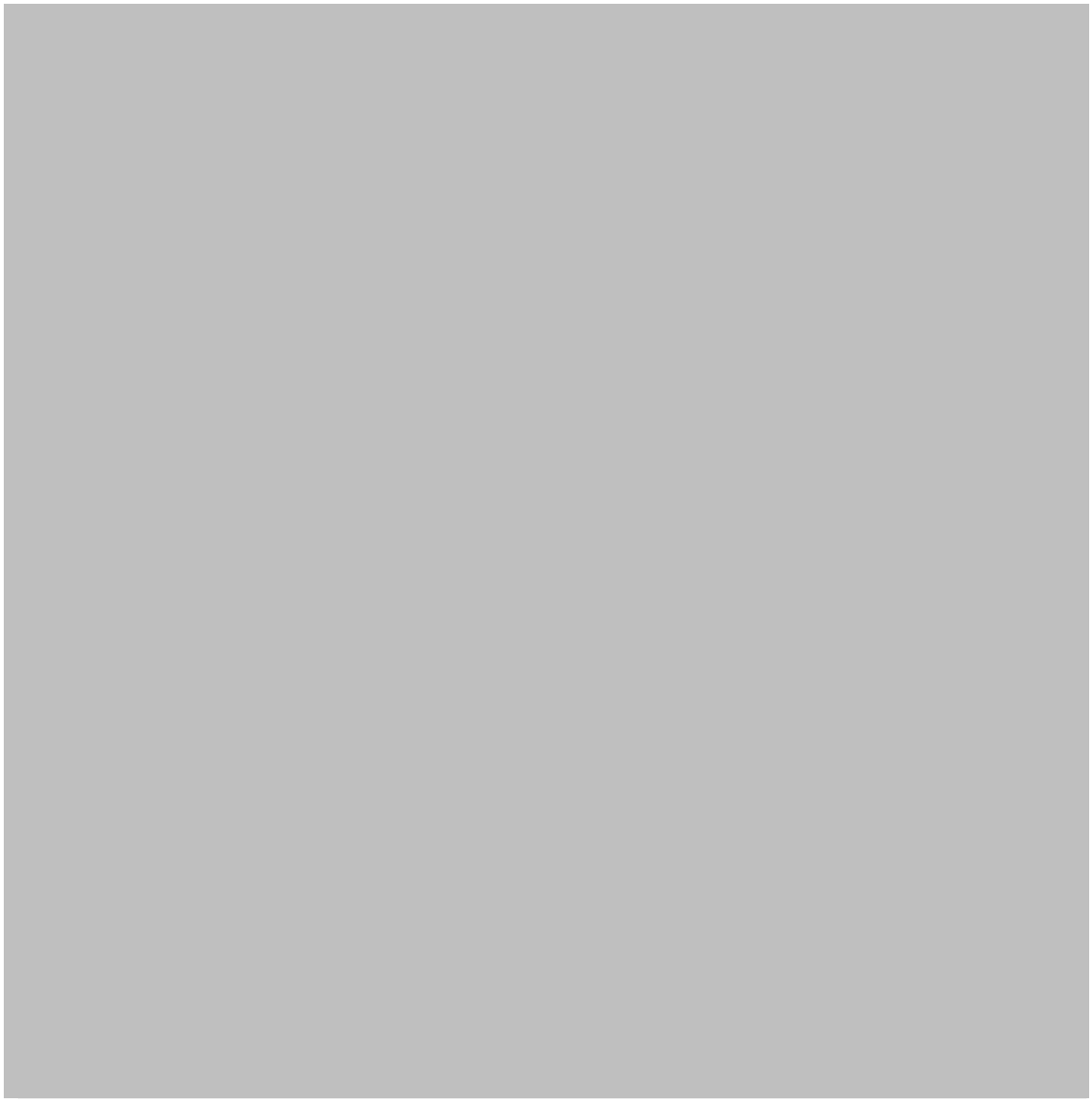
Pittsburgh Sleep Quality Index (PSQI)





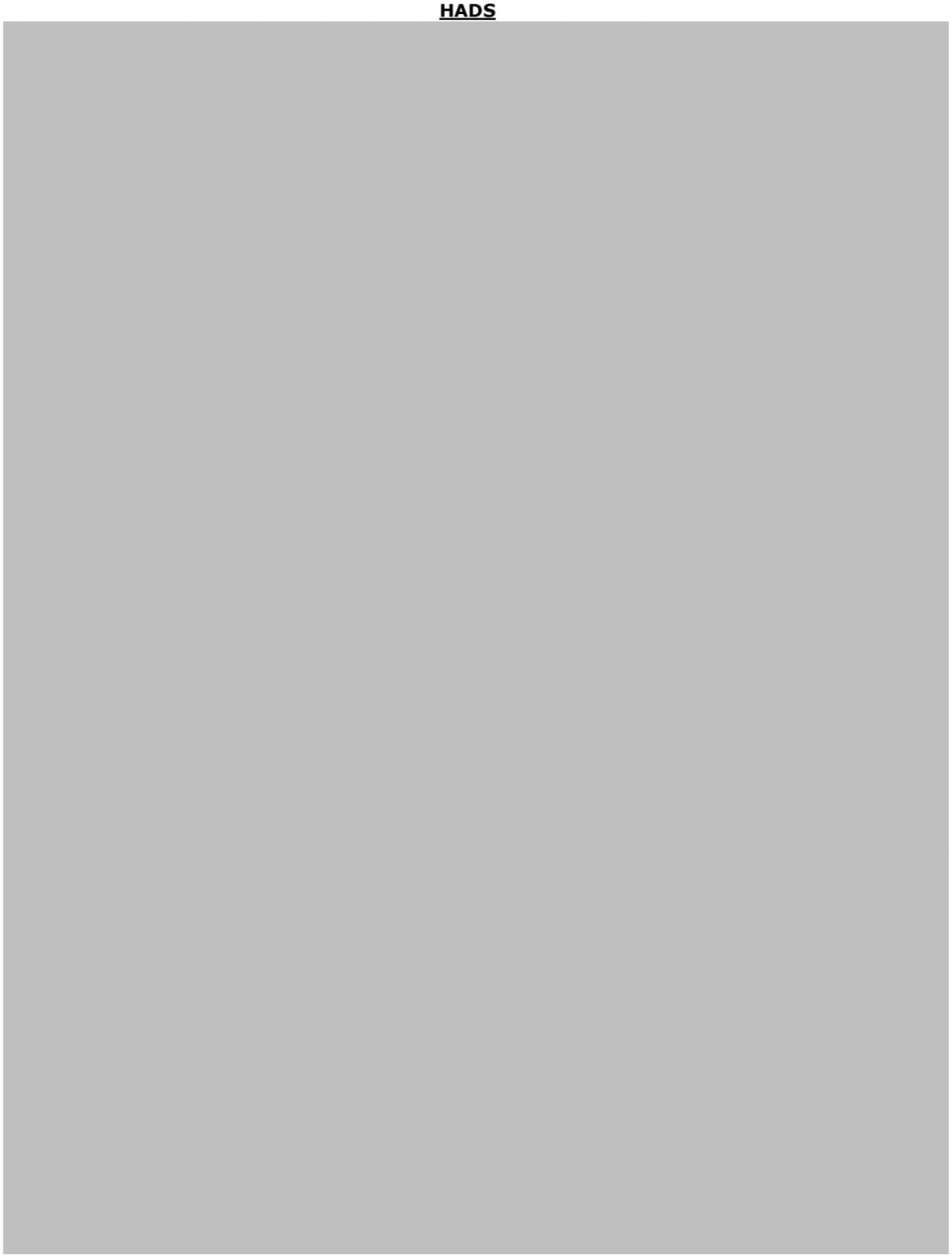
Appendix 2b

Epworth Sleepiness Scale



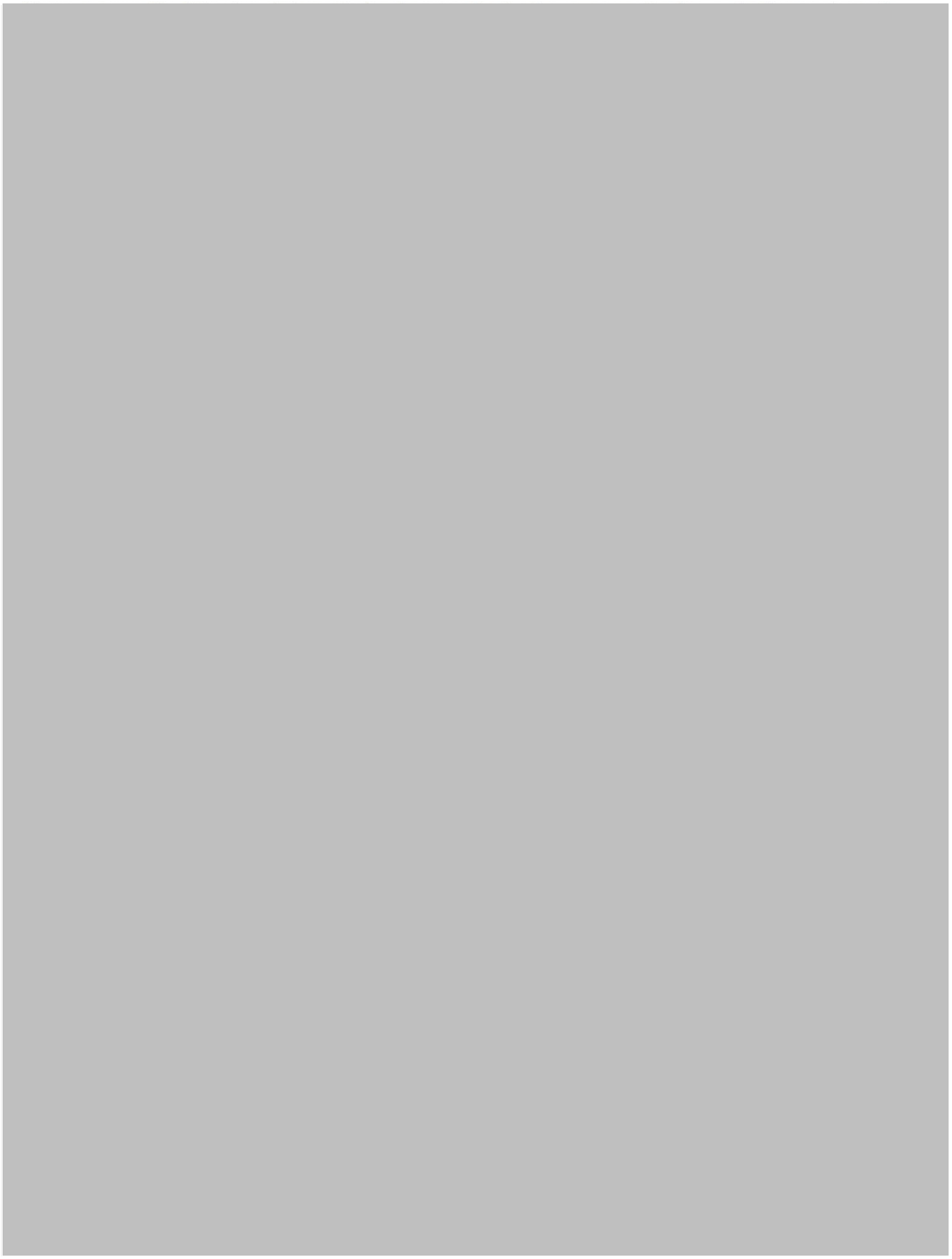
Appendix 3c

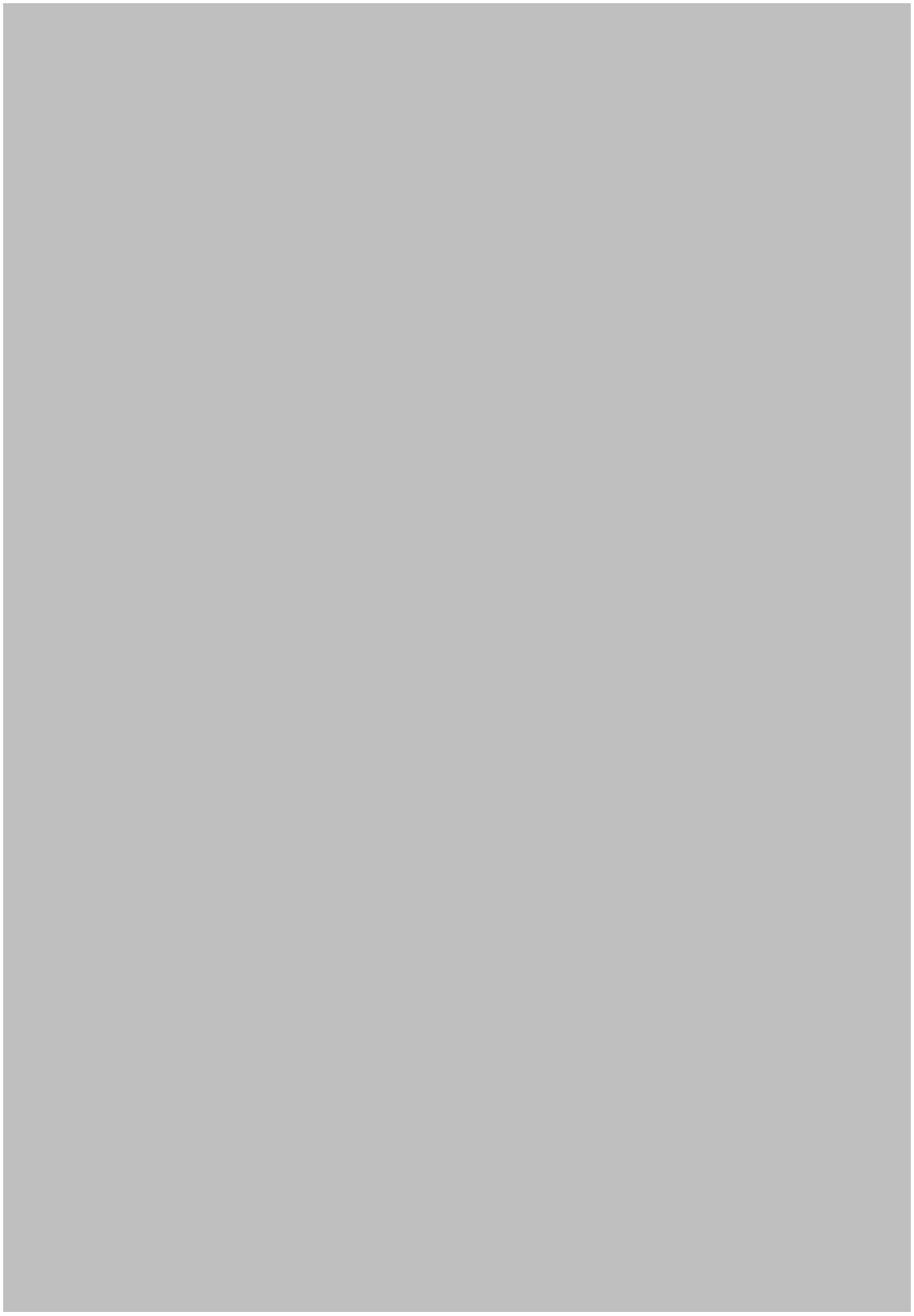
HADS



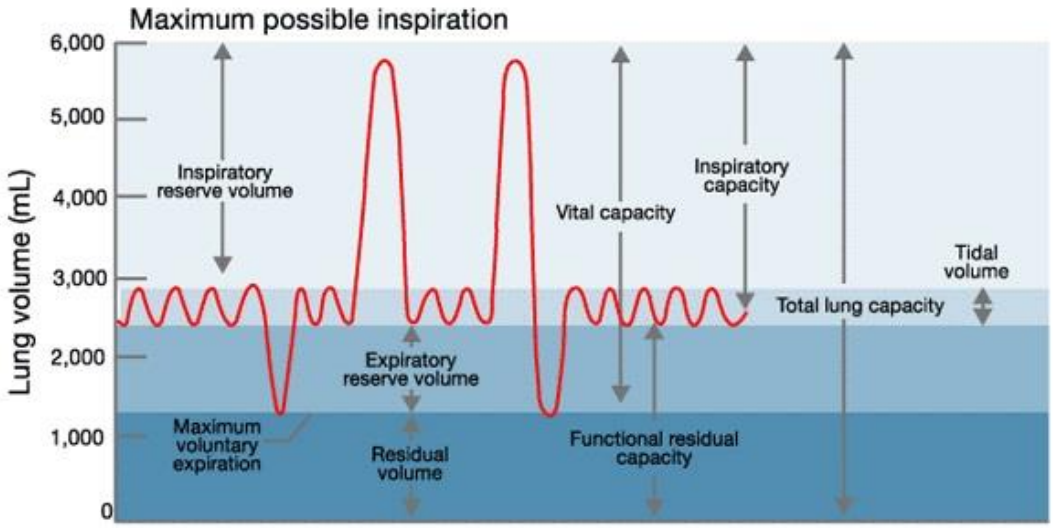
Appendix 4d

Impact of Weight on Quality of life Questionnaire (IWQOI-Lite)





C) Standard (static) lung volumes as measured with a spirometer (*Chapter 4)*



D) MEDLINE search strategy used to identify studies for systematic review (*Chapter 4)*

1. exp Sleep Apnea Syndromes/
2. (sleep$ adj3 (apnea$ or apnoea$)).mp.
3. (hypopnea$ or hypopnoea$).mp.
4. OSA.mp.
5. SHS.mp.
6. OSAHS.mp.
7. or/1-6
8. lifestyle.mp.
9. exercise.mp.
10. weight loss.mp.
11. weight.mp.
12. physical activity.mp.
13. or/8-12
14. 7 and 13

Filter to identify RCTs

1. exp "clinical trial [publication type]"/
2. (randomised or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.
8. or/1-7
9. Animals/
10. Humans/
11. 9 not (9 and 10)
12. 8 not 11

The MEDLINE strategy and RCT filter are adapted to identify trials in other

electronic databases