A thesis submitted for the degree of Doctor of Philosophy

OBESITY AND SLEEP

Monash University

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Obesity and Sleep

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BMedSc (Hons)

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Abstract

Background Given that obesity is increasing globally, it is important to understand its consequences for health. In the last few decades, there has been tremendous progress in studies evaluating the effect of obesity on a range of health outcomes, such as cardiovascular health, diabetes, disability, and cancer. However, less is known about obesity-related sleep problems.

Aims The primary aim of this PhD is to assess the relationship between obesity and excessive daytime sleepiness, and the potential impact of weight loss interventions on daytime sleepiness. The secondary aim of this PhD is to assess the effect of weight loss interventions on another measure of sleep, use of sleep medications. To place sleep problems in the context of the overall burden of disease, this PhD also aimed to assess the impact of sleep problems on disability and mortality over the life-course.

Methods Six studies with six different methodologies, were performed to answer the research questions in this PhD. The first study was a cross-sectional study of the general working population in Melbourne, Australia (The Global Corporate Challenge® Evaluation Study, n = 707), to confirm the association between obesity and excessive daytime sleepiness, and to identify the prevalence, and other correlates of, excessive daytime sleepiness. The second study assessed the relationship between weight change and daytime sleepiness, and its mediating pathways, through a causal framework, using a five-year prospective cohort study of community-dwelling older American adults (the Sleep Heart Health Study, n = 1,468). The third study was a systematic review and meta-analysis to estimate the effect of participation in weight loss interventions (n = 42) on daytime sleepiness. The fourth study assessed the short- and long-term impact of a workplace physical activity intervention on daytime sleepiness, in a cohort of general working population in Melbourne, Australia (The Global Corporate Challenge® Evaluation Study, n = 685). The fifth study assessed the change in use of sleep medications following weight loss through gastric bypass surgery and intensive lifestyle modification in 32,599 obese adults in Sweden, using nation-wide registry data linkage (Scandinavian Obesity Surgery Registry, Itrim health database, and Prescribed Drug Register). The final study used the Wisconsin Longitudinal Study dataset (n = 4,980), a life-course study dataset of high school graduates from the state of Wisconsin (U.S.) in 1957, to assess the likelihood of developing disability and the risk of mortality associated with chronic excessive daytime sleepiness. The implications over the life course on life expectancy were additional estimated.

Results In the first study, we found that approximately one in six Australian workers had excessive daytime sleepiness. We identified a cross-sectional association between obesity and excessive daytime sleepiness, with both sharing a range of risk factors, including markers of poor dietary behaviour and poor mental health. In the second study, we found that weight gain was associated with worse daytime sleepiness over five years for women, but not men. Approximately one-fifth of the relationship between weight change and daytime sleepiness was mediated through severity of obstructive sleep apnea. In the third study, we found that weight loss interventions improved daytime sleepiness, to a larger degree in surgical, than non-surgical studies. There was a dose-response relationship between the amount of weight loss and the magnitude of improvement in daytime sleepiness. In the fourth study, among those with excessive daytime sleepiness at baseline, we found an immediate and sustained long-term improvement in daytime sleepiness following participation in a workplace pedometer-based physical activity program. The degree of improvement in daytime sleepiness was associated with the amount of reduction in body mass index. In the fifth study, contrary to our hypothesis, we found that use of sleep medications increased up to five years after weight loss through gastric bypass surgery, compared to intensive lifestyle modification. However, there was no evidence for a dose-response relationship between the amount of weight loss and the degree of increase in sleep medication use for either of the treatment groups. In the sixth study, we found that chronic excessive

daytime sleepiness was associated with a higher likelihood of developing disability over 7 years and higher risk of 10-year mortality. Individuals with chronic excessive daytime sleepiness at age 60 lived 3 years less overall, and 3 years less disability-free, compared to their non-sleepy counterparts.

Conclusion There is consistent, strong, evidence for the role of obesity in excessive daytime sleepiness, as well as for the potential benefit of weight loss in the improvement of daytime sleepiness. The finding of increased use of sleep medications following gastric bypass surgery was unexpected and requires further investigation. Having chronic excessive daytime sleepiness was associated with increased likelihood of developing disability, increased risk of mortality, and reduced overall as well as disability-free life expectancy. The findings from this PhD: (i) provide a clearer understanding of the relationship between obesity and markers of sleep, (ii) further emphasise the importance of weight loss and maintenance in those who are overweight or obese, and (iii) highlight the potential impact of sleep problems on overall health at older ages.

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I would like to extend my sincerest gratitude and appreciation to Anna Peeters, my main PhD (and honours) supervisor. The commencement of my PhD candidature would not have been possible without her help, both in terms of administrative and mental support. During my five years as Anna's student, Anna has not only helped me develop a strong foundation in epidemiology and biostatistics, but has also provided me with numerous opportunities to bring my research to a higher level, be it through attending various professional development courses, conferences, or collaborating with international institutions. She motivates, encourages, and facilitates learning, but allows sufficient space for self-development. Her plan for me was well thought out and well-paced, ensuring that towards the end of my candidature, I would gradually require less support from her, becoming an independent researcher. What I value most from my time with Anna is learning how she conducts herself, as a supervisor, a mentor, a leader, and a parent; which I find inspiring and I believe, requires no further description to those who know her. Everytime I find myself in a difficult position I would ask myself "What would Anna do?"; this frame of thinking has helped me solve a majority of all the academic and personal problems I have encountered in the past few years, and I believe also for the years to come. Anna is to me, a teacher, a role model, and an inspiration. I always say that I have probably used up a lifetime's worth of luck, meeting her. She inspired me to be a better researcher, and more importantly to be a better person. Perhaps the only way to repay the debt is to try and become somone else's Anna.

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General Declaration

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

This thesis includes three original papers published in peer reviewed journals and three submitted publications. The core theme of the thesis is obesity and sleep. The ideas, development and writing up of all the papers in the thesis were the principal responsibility of myself, the student, working within the Global Obesity Centre at Deakin University; and the clinical diabetes and epidemiology unit at Baker Heart and Diabetes Institute under the supervision of Prof Anna Peeters and Prof Jonathan Shaw.

The inclusion of co-authors reflects the fact that the work came from active collaboration between researchers and acknowledges input into team-based research.

In the case of Chapters 3-8, my contribution to the work involved the following:

Thesis chapter	Publication title	Status	Nature and % of candidate's contribution	Co-author name(s) Nature and % of Co-author's contribution	Co-author(s), Monash Student Y/N
3	The prevalence and characteristics associated with excessive daytime sleepiness among Australian workers	Published	80%	**Rosanne Freak-Poli** Study design, literature synthesis, critical interpretation of the data, drafting manuscript **Anna Peeters** Study design, literature synthesis, statistical analysis, critical interpretation of the data, drafting manuscript	N for all
4	The relationship between weight change and daytime sleepiness: The Sleep Heart Health Study	Under review (2nd round of revision)	80%	**Liliana Orellana** Study design, statistical analysis, integrity of the data and accuracy of the data analysis, critical interpretation of data, drafting manuscript **Jonathan Shaw** Study design, critical interpretation of	N for all

				data, drafting manuscript **Evelyn Wong** Study design, critical interpretation of data, drafting manuscript **Anna Peeters** Study design, statistical analysis, integrity of data and accuracy of the data analysis, critical interpretation of the data, drafting manuscript	
5	Does intentional weight-loss improve daytime sleepiness? -- A systematic review and meta-analysis	Published	80%	**Christopher Stevenson** Drafting protocol, data extraction, statistical analysis, accuracy of data analysis, critical interpretation of data, drafting manuscript **Evelyn Wong (5%), Tara Boelsen-Robinson (5%), and Stephanie Tanamas** Drafting protocol, data extraction, critical interpretation of the data, drafting manuscript **Jonathan Shaw, Matthew Naughton, and John Dixon** Drafting protocol, criticial interpretation of the data, drafting manuscript **Anna Peeters** Drafting protocol, literature search, data extraction, data matching, statistical analysis, critical	N for all but Evelyn Wong and Tara Boelsen-Robinson

				interpretation of the data, drafting manuscript	
6	The immediate and long-term changes in daytime sleepiness after participation in a workplace pedometer program – a prospective cohort study	Published	70%	**Rosanne Freak-Poli** Study design, literature synthesis, critical interpretation of the data, drafting manuscript **Chris Stevenson** Statistical analysis, critical interpretation of the data, drafting manuscript **Anna Peeters** Study design, literature synthesis, statistical analysis, critical interpretation of the data, drafting manuscript	N for all
7	Change in use of sleep medications after gastric bypasss surgery or intensive lifestyle treatment in obese adults	Submitted	70%	**Anna Peeters** Study design, statistical analysis, critical interpretation of the data, drafting manuscript **Ingmar Näslund, Johan Ottosson, and Kari Johansson** Data collection, critical interpretation of the data, drafting manuscript **Claude Marcus** Critical interpretation of the data, drafting manuscript **Jonathan Shaw** Study design, criticial interpretation of the data, drafting manuscript **Gustaf Bruze** Study design, statistical analysis, integrity of the data and accuracy of the	N for all

				data analysis, critical interpretation of the data, drafting manuscript **Johan Sundström** Statistical analysis, critical interpretation of the data, drafting manuscript **Martin Neovius** Study design, data collection, statistical analysis, integrity of the data and accuracy of the data analysis, critical interpretation of the data, drafting manuscript	
8	The relationship between excessive daytime sleepiness, disability, and mortality, and its implications on life expectancy	Submitted	80%	**Jonathan Shaw** Study design, statistical analysis, criticial interpretation of the data, drafting manuscript **Anna Peeters** Study design, statistical analysis, integrity and accuracy of the data analysis, critical interpretation of the data, drafting manuscript	N for all

I have renumbered sections of submitted or published papers in order to generate a consistent presentation within the thesis.

Student signature: _____ [redacted] _____ **Date:** 17/03/2017

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the student's and co-authors' contributions to this work. In instances where I am not the responsible author I have consulted with the responsible author to agree on the respective contributions of the authors.

Main Supervisor signature: _____ [redacted] _____ **Date:** 17/03/2017

List of abbreviations and acronyms

AHI	Apnea-hypopnea index
BMI	Body mass index
CI	Confidence interval
CPAP	Continuous positive airway pressure
CVD	Cardiovascular disease
DAG	Directed acyclic graph
DDDs	Defined daily doses
EDS	Excessive daytime sleepiness
ESS	Epworth sleepiness scale
GCC	Global Corporate Challenge
HR	Hazard Ratio
K10	Kessler 10
MET	Metabolic equivalent
NCDs	Noncommunicable diseases
NDE	Natural direct effect
NIE	Natural indirect effect
OAHI	Obstructive apnea-hypopnea index
OR	Odds ratio
OSA	Obstructive sleep apnea
RCI	Reliable change index
RCT	Randomised controlled trial
RDI	Respiratory disturbance index
RTM	Regression to the mean

SD	Standard deviation
SEIFA	Socio-Economic Indexes for Areas
SF-12	Short Form-12
SF-36	Short Form-36
SHHS	Sleep Heart Health Study
TE	Total effect
WHO	World Health Organization

CHAPTER 1

Introduction

The global prevalence of obesity has more than doubled since 1980.[1] Full understanding of its impact on our health and quality of life is therefore important. There has been excellent progress in areas such as cardiovascular health, diabetes, disability, and cancer; but less in the area of sleep health, despite its essential role in our daily life.

> *"Sleep!" said the old gentleman, "He's always asleep. Goes on errands fast asleep, and snores as he waits at table."*
>
> *-to Joe, the 'wonderfully fat-boy' in the Pickwick Papers by Charles Dickens*

The idea that obesity causes sleep-disordered breathing has long been hypothesised; one of the earliest detailed descriptions of this relationship was believed to have come from Charles Dickens, in his work "The Pickwick Papers".[2] Various longitudinal studies and randomised controlled trials that followed have successfully provided evidence for this relationship.[3-6] Obesity was later found to be associated with other sleep disorders such as insomnia and restless leg syndrome,[7-9] and also with conditions such as short sleep duration,[10,11] excessive daytime sleepiness[12-14] and use of sleep medications[15]; but the strength of evidence in these areas were not clear. This thesis focuses on the relationship between obesity and aspects of sleep that are readily measureable in a wide range of settings, specifically daytime sleepiness and use of sleep medications.

Part 1 of this thesis assesses the relationship between obesity and excessive daytime sleepiness. My research begins with a cross-sectional study to confirm the association between obesity and excessive daytime sleepiness in a general working population in Australia (chapter 3). I subsequently assess the potential effect of weight change on daytime sleepiness, and the pathways through which it occurs, through a causal framework, in a cohort of community-dwelling American adults (chapter 4). Acknowledging the limitations of findings from observational studies, especially one related to unintentional weight loss, I proceed to perform a systematic review and meta-analysis to assess the effect of weight loss interventions on daytime sleepiness, and a meta-regression to assess the potential dose-response relationships between the magnitude of weight change and daytime sleepiness (chapter 5). Using available data, I further assess the likely short- and long-term change in daytime sleepiness following a 4 month, workplace pedometer-based physical activity program in Australian adults, and the potential role of weight change in this effect (chapter 6).

I hypothesised that other sleep measures, such as use of sleep medications, would respond similarly to weight loss. Therefore, in Part 2 of this thesis, I perform a novel nationwide matched cohort study on the use of sleep medications following gastric bypass surgery and intensive lifestyle modification in those with obesity, using Swedish registry data, to confirm my hypothesis (chapter 7). In addition to studying the relationship between obesity and sleep measures, I also aimed to further describe the burden associated with having sleep problems. Therefore, in Part 3 of this thesis, I perform a study to assess the likelihood of developing disability and the risk of mortality associated with having excessive daytime sleepiness, and the implication of these relationships on life expectancy (with or without disability) at age 60 (chapter 8).

The series of studies conducted in this thesis aimed to provide further understanding on the potential effect of obesity on sleep measures, the role of weight loss in mitigating obesity-related sleep problems, and the impact of having sleep problems on disability, mortality risk and life expectancy. Further understanding on the causal relationship between obesity and sleep problems will give a more comprehensive view to the overall consequences of obesity on health, which in turn helps determine the extent to which obesity is a global health problem. If evidence for the potential benefit of weight loss on sleep measures is found, it may further motivate the promotion of weight loss interventions for obese individuals; and adds to the confidence of choosing weight loss interventions as an option for treating sleep problems. The assessment of incident disability, mortality risk and life expectancy associated with having sleep problems, provides a

readily comprehensible form of information to the general public and health practitioners, regarding the consequences of poor sleep, which may improve current underrecognition of sleep as an important health factor in society.

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CHAPTER 2

Literature Review

2.1. Obesity

2.1.1. Definition and measurement

Obesity refers to a state of excessive fat accumulation that may be harmful to one's health.[1] There are various ways to assess body fat,[2] the 'best' of which remains under debate. Tools such as computed tomography, magnetic resonance imaging, and dual-energy x-ray absorptiometry provide reliable estimates to (total) body fat and are often regarded as the reference methods in validation studies.[2-5] However, they may not be suitable for use in large scale epidemiologic studies, mainly due to cost and technical limitations. The more convenient and low-cost anthropometric tools, mainly body mass index and waist circumference, are usually the preferred choice.[2]

Body mass index (BMI) is calculated as weight in kilograms divided by the square of height in metres (kg/m^2).[2] Height can be measured through a stadiometer or a tape measure; and weight through a portable or balance beam scale in light or no clothing.[6] Both components of BMI can be easily and quickly measured in clinics or reported by study participants/ patients themselves. Measurement for waist circumference is taken with a tape measure in a standing position, at end of expiration, with light or no clothing.[2] Measuring waist circumference can be more challenging than measuring weight and height for BMI because measurement sites for waist circumference may vary quite widely. In 2011, through a systematic review, Ross et al. identified eight different waist circumference measurement protocols (mid-point of lowest rib and iliac crest, minimal waist circumference, immediately above iliac crest, umbilicus, 1 inch above the umbilicus, 1 cm above the umbilicus, at the lowest rib, and largest abdominal circumference) in studies assessing the relationship between waist circumference with morbidity and mortality.[2,7] **Table 1** shows the international cut-off points for BMI and waist circumference recommended by the World Health Organization.[8]

Both BMI and waist circumference are sensitive measures of high-risk adiposity. However, waist circumference may be superior to BMI in cases where the differentiation between fat and lean mass is important. For instance, in athletes or body builders with large muscle mass; and in detecting change in level of adiposity in elderly population where there is differential loss of lean mass. On the other hand, BMI may be superior to waist circumference in more severe cases of obesity, when locating anatomical structures as references point for measuring waist circumference may become quite challenging. Measurement of BMI also requires less training. This could be one of the major reasons why despite of its aforementioned limitations, BMI remains the preferred choice in clinics and large population studies.[2]

2.1.2. Causes

It is widely acknowledged that obesity results from the imbalance between energy intake and expenditure, mainly driven by excessive or unhealthy diet and/or inadequate physical activity in the long-term.[9] However, in the last few decades, researchers have found evidence suggesting that diet and physical activity may not be the only two determinants of obesity.[10]

Table 1. International (a) BMI and (b) waist circumference cut-offs recommended by the World Health Organization.

(a)

Categories	Body mass index (kg/m^2)
Underweight	<18.5
Normal weight	18.5-24.9
Overweight	25.0-29.9
Obese	⩾30
Obese class I (moderate)	30-34.9
Obese class II (severe)	35.0-39.9
Obese class III (very severe)	⩾40.0

(b)

Categories	Waist circumference (cm), Female	Waist circumference (cm), Male
Low risk	<80.0	<94.0
Increased risk	80.0-87.9	94.0-101.9
Substantially increased risk	⩾88.0	⩾102.0

Adapted with permission, from World Health Organization. Obesity: Preventing and Managing the Global Epidemic of Obesity. WHO Report, Geneva, 2000. Table 2.1 on page 9 and Table 2.2 on page 10. Available at http://www.who.int/nutrition/publications/obesity/WHO_TRS_894/en/ [8]

For instance, genetics can have a substantial role in people's susceptibility to weight gain. This idea was introduced in 1977, when a study on 250 monozygotic and 264 dizygotic male veteran twin pairs, showed for the first time that human obesity may have moderate to high heritability.[11,12] A later study in 1986 showed that weight of adopted children were more closely correlated with their biological, rather than foster parents; further confirming the hypothesis.[12,13] Robust evidence for the role of genetics in obesity was seen in 2007, through the discovery of *FTO* gene from the Genome-Wide association study.[14] A recent meta-analysis on 339,224 individuals identified 97 loci that may be associated with obesity, measured though BMI.[15]

Sedentary behaviour, the act of prolonged sitting, can be another important determinant of obesity. Studies have shown that longer periods of sedentary behaviour predict higher risk of obesity, even after adjusting for levels of physical activity; although findings have not been very consistent[16], potentially attributable to the different methods of measurement for both obesity and sedentary behaviour. A more recent study by Bell et al. suggests that when assessed independently, high physical activity and low leisure sitting time did not reduce the risk of incident obesity over 5 years; but when combined, a significant protective effect was observed (OR = 0.26 (95%CI 0.11 – 0.64)).[17]

Short sleep has been associated with greater risk of obesity, perhaps more consistently in children than in adults.[18,19] It is hypothesised that short sleep can cause obesity through increased caloric

intake from increased opportunity to eat and hunger (associated with lower leptin and higher ghrelin) and/or through reduced energy expenditure from altered thermoregulation and increased fatigue (**Figure 1**).[20,21]

Other potential contributors to obesity, according to McAllister et al, include infections, epigenetics, maternal age, prescription medications, reproductive fitness, assertive mating, endocrine disrupters, ambient temperature, and intrauterine and intergenerational effects; which may act independently or interact with diet and physical activity, to cause obesity.[10]

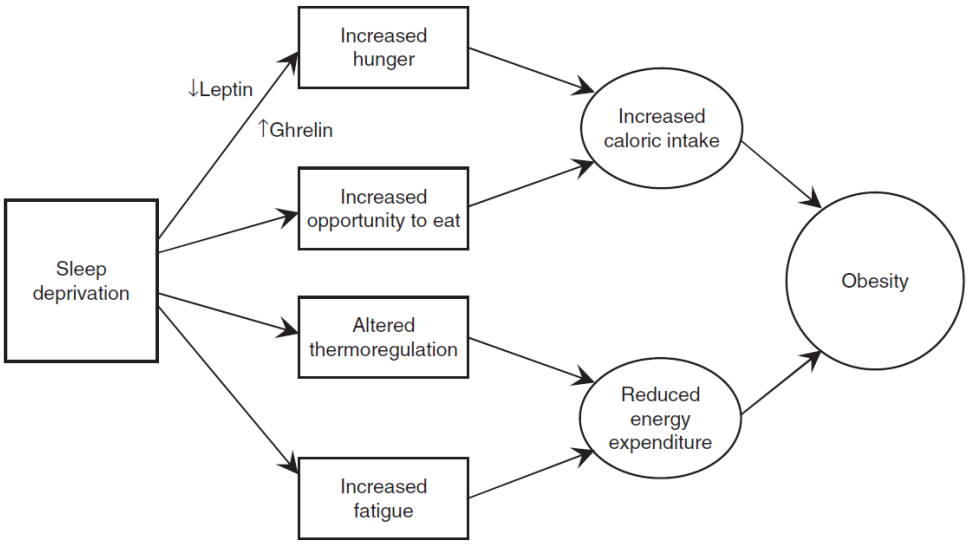


Figure 1. Potential pathways through which sleep duration causes obesity

Taken from Patel SR, Hu Fb. Short Sleep duration and weight gain: a systematic review. Obesity (Silver Spring). 2008 Mar;16(3):643-53,[20] reproduced with permission of the rights holder, *John Wiley and Sons* (License number 4045061101395).

2.1.3. Consequences and significance

> *"Corpulency, when in an extraordinary degree, may be reckoned a disease, as it in some measure obstructs the free exercise of the animal functions, and hath a tendency to shorten life, by paving the way to dangerous distempers."*
>
> *- Flemyng, 1760*

The notion that obesity is largely a cosmetic problem, with minimum clinical significance, cannot be more wrong.[22-24] Obesity results in a wide range of health problems, from psychological disoders to cancer.

Obesity, through increased fat mass around the neck, may exert mechanical pressure on the upper airway, causing obstructive sleep apnea (see section 2.3.1). [25,26] Similarly, the increased mechanical pressure from fat mass on the bones and joints, predisposes to osteoarthritis of the knees and ankles.[26,27] Increased fat mass may also cause psychological distress from the social stigma against obesity, especially in women.[26,28]

The fat cells, through releasing hormones and inflammatory cytokines, may lead to a series of disoders. The most well known obesity-related endocrine disorder is type 2 diabetes. Obesity, perhaps through the release of free fatty acids and other adipocytes, causes insulin resistance. When insulin resistance combines with an insulin secretory disorder, type 2 diabetes ensues.[24,26,29] Through the release of adipocytes such as the prothrombin activator inhibitor-1, free-fatty acids, angiotensinogen, leptin, and other inflammatory cytokines, obesity may lead to hypertension.[30,31] Hypertension and type 2 diabetes, together with dyslipidemia, predisposes to cardiovascular diseases.[26,31] Other consequences of obesity include gallbladder disease, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, and cancer.[26] The potential consequences of obesity on sleep disorders other than obstructive sleep apnea is discussed further in section 2.3.1.

The world prevalence of obesity has been increasing, from 3.2% (men) and 6.4% (women) in 1975 to 10.8% (men) and 14.9% (women) in 2014.[32] In Australia, the prevalence of obesity was 28.4% in men and 27.4% in women in 2014.[33] Given the known consequences of obesity on our overall health, quality of life and well-being,[24,26] as well as the impact of obesity on health care costs,[34] a concerted effort across various public health, epidemiology and clinical disciplines is needed to help monitor, prevent and manage obesity.

2.1.4. Prevention

Maintaining adequate levels of physical activity and a healthy diet may keep energy balance in check and help prevent obesity.

Table 2 summarises the physical activity and dietary guidelines recommended by the World Health Organization.[35,36]

> *"If we could give every individual the right amount of nourishment and exercise, not too little and not too much, we would have found the safest way to health."*
>
> *-Hippocrates*

Although maintaining adequate level of physical activity and healthy diet is a personal responsibility, it has become increasingly challenging in today's obesogenic (obesity-condusive) environment.[37] With the advancement of technology in the last few decades, jobs now require much lower levels of physical activity,[38] supporting more sedentary roles. There is also increasing availability and variety of "junk food" and sugar-sweetened beverages; both of which contribute to obesity. [39,40] The role of environment in the incidence of obesity is irrefutable. Countries with a more obesogenic environment, such as the United States (**Figure 2**), have higher prevalence of obesity.[32] Making healthy individual choices now requires greater determination and effort compared to decades ago. Obesity prevention strategies need to focus not only on individual choices, but also on creating a less obesogenic environment to facilitate individual change.[41]

2.1.5. Treatment

Individuals with obesity are recommended to lose weight, to resolve or manage obesity-related comorbidities. There are several ways to achieve weight loss, the three major intervention categories are lifestyle modification, pharmacological intervention, and bariatric surgery. Lifestyle modification is always recommended to those overweight or obese, whilst pharmacological intervention and bariatric surgery should be chosen carefully with consideration of the individual's degree of obesity, financial capacity, personality and other health conditions.

Lifestyle intervention mostly involves change in diet and physical activity, alone or in combination, with varying intensity.[45] Conventional dietary interventions can involve low-calorie diet, low-fat diet, low-carbohydrate diet, low-glycemic load diet or Mediterranean diet;[45] whereas more intensive ones include meal replacement therapy which produces substantially more weight loss than conventional diet intervention (approximately 2.5 kg more, according to a meta-analysis of 6 randomized controlled trials).[45,46] Conventional physical activity interventions can involve running, aerobic exercise or even brisk walking to increase daily steps. Evidence so far suggests that the benefit of physical activity on weight loss is fairly limited but is essential for maintenance of weight loss, and may have cardiovascular benefits independent of weight loss.[45]

Figure 2. Typical cafetaria school lunches in USA, France, Greece, and South Korea

A typical cafeteria school lunch in: the USA (top left image), contains fried chicken, mashed potatoes, peas, fruit cup, and a chocolate chip cookie; in France (top right image), contains steak, carrots, green beans, cheese, and fresh fruit; in Greece (bottom left image), contains baked chicken, orzo, stuffed grape leaves, tomato and cucumber salad, fresh oranges, and greek yogurt with pomegranate seeds; in South Korea (bottom right image), contains fish soup, tofu, rice, kimchi, and fresh vegetable. More images from other countries around the world are available in Sweetgreen's webpage.[42]

Pictures were taken from http://sweetgreen.tumblr.com/post/103458679563/school-lunches-around-the-world, with permission from rightsholder, Sweetgreen®.

Table 2. Physical activity and diet recommendations by the World Health Organization

Age group	Physical activity recommendation	Dietary recommendation
5-17 years	60 minutes of moderate-to-vigorous intensity physical activity per day. For at least three days per week, involve muscle- and bone-strengthening activities. Daily physical activity must be mostly aerobic.	• Daily intake of fat to be kept under 30% of total energy intake. Avoid saturated fats and industrial trans fats. • Daily intake of free sugars to be limited to less than 10% of total energy intake (i.e. 50 g for a healthy person consuming 2000 calories/day) and avoid taking more than 5 g (approx. 1 teaspoon) of salt per day. Use of iodized salt is preferred. • Take 400g (approx. 5 portions) or more of fruits and vegetables per day. Legumes, nuts and whole grains are also part of healthy diet.
18-64 years	150 minutes of moderately intense physical activity or 75 minutes of vigorous physical activity in a week, or equivalent. The activities may be broken down into bouts of at least 10 minutes duration. For at least two days per week, involve muscle strengthening activities for major muscle groups.	
65 years and above	150 minutes of moderately intense physical activity or 75 minutes of vigorous physical activity in a week, or equivalent. The activities may be broken down into bouts of at least 10 minutes duration. For at least three days per week, involve activities that enchance balance and prevent falls. For at least 2 days per week, involve muscle-strengthening activitives for major muscel groups. When the ability to meet guideline is limited by health conditions, it is recommended to move according to the maximum of their capacity.	

Source: Global recommendations on physical activity for health, and health diet fact sheet, both from the World Health Organization [35,36]

Physical activity can be light, moderate or vigorous; which can be defined objectively through 'Metabolic Equivalents';[43] or more practically through the talk test (light = singing is possible, moderate = conversation is possible, but not singing, vigorous = conversation is not possible). [44]

Pharmacological approaches to weight loss started as early as 1890s, when sheep thyroid extract was used as a medication for weight loss in people with normal thyroid function; but this approach was soon abandoned as it was associated with cardiac arhythmias and deaths. Similarly, other medications, such as 2,4-dinitrophenol, amphetamine, diuretics, laxatives, fenfluramine/phentermine, and sibutramine were later found to have weight loss properties, but given their side effects, are now withdrawn from the market (or remains in market but no longer

indicated for weight loss). The current list of anti-obesity medications approved by the US Food and Drug Administration includes orlistat, lorcaserin, phentermine/topiramate, naltrexone/bupropion and liraglutide. A recent review by Daneschvar et al., summarised the conditions under which the use of a particular anti-obesity medication is favoured over the other. For example, orlistat results in a relatively small amount of weight loss (5.8-6.7 kg), and may have benefiticial effect on total and LDL cholesterol levels, independent of weight loss. Therefore, orlistat may be recommended for those with mild obesity and metabolic syndrome. Lorcaserine produces a similar level of weight loss and was found to decrease total cholesterol and triglycerides level; but is only effective for the first few months and may increase the risk of cancers. Hence, lorcaserine may be suitable for those seeking short-term anti-obesity treatment, and who have risk factors for cancer (schwannoma, astrocytoma, squamous cell carcinoma, breast fibroadenoma, and breast adenocarcinoma). The phentermine/topiramate combination produces a greater degree of weight loss (8.1-10.2 kg) and may also benefit the lipid profile, but the risk of anxiety and depression must be noted. The naltrexone/bupoprion combination is the preferred option for patients with tobacco-addiction problem. Liraglutide can be recommended for patients requiring better lipid profile and lower blood glucose level[47] A recent study in the LEADER trial showed evidence for cardiovascular benefits from use of liraglutide.[48]

Bariatric surgery is the recommended procedure for individuals with more severe obesity. According to the National Institutes of Health consensus in 1992,[49] which remains the most widely used guideline for bariatric surgery to date, bariatric surgery may be recommended to individuals with BMI of 40 kg/m^2 and above or between 35-40 kg/m^2 with at least one severe comorbidity such as diabetes mellitus, cardiovascular diseases and obstructive sleep apnea. Bariatric surgery is traditionally known to help produce weight loss mainly through restriction of food intake, through malabsorption of nutrients, or through a combination of restriction and malabsorption. In recent years, it is hypothesised that other factors such as alteration of bile acids, gut hormones, and hormones produced by adipose tissue, may also have a role in post-operative weight loss. [50] According to the American Society for Bariatric and Metabolic Surgery, the four most common types of bariatric surgeries are: gastric bypass, sleeve gastrectomy, adjustable gastric band, and biliopancreatic diversion with duodenal switch.[51] The degree of weight loss differs between different types of weight loss surgery procedures; and each procedure has its own unique sets of advantages and disadvantages, which are summarised in **Table 3**.

2.2. Sleep

2.2.1. Definition and physiology

For hundreds of years we were led to believe that sleep is simply a passive state of unconsciousness where all activities are temporarily suspended. Following a deeper understanding in the physiology of sleep, especially the discovery of sleep stages and cycles, we came to understand the active nature of sleep.[52]

During sleep, we go through cycles of rapid eye movement (REM) and non-rapid eye movement (NREM). As the name suggests, REM stage involves rapid eye movement which can be detected through an electrooculogram and also skeletal muscle paralysis (atonia), which can be assessed through an electromyogram. It can be difficult to distinguish REM stage from wakefulness stage through an electroencephalogram as they present an almost identical beta wave. The NREM stage can be further divided into four stages. NREM stage 1 (somnolence/ drowsy) is characterized by

theta waves in an electroencephalogram. Sudden twitches and limb jerks may be observed at this stage. NREM stage 2 involves sleep splindles (short bursts of activity) and K-complexes (high amplitude and low frequency events) in the electroencephalogram. Level of muscular activity decreases, and conscious awareness to external environment diminishes. Stage 3 and 4 (deep/ slow wave sleep) involves delta and theta waves in the electroencephalogram (**Figure 3**). [52]

The proportion of slow wave sleep in a sleep cycle decreases with longer duration of sleep, whilst the reverse is true for REM sleep. 25% of human sleep consists of REM sleep. The REM stage is more active than the stages of NREM; measurements may vary but generally involve higher breathing rate, heart rate, blood pressure and more blood flow to the brain than NREM stage. Due to the generally more 'active' characteristic of REM stage, it is often referred to as 'paradoxical sleep'. [52]

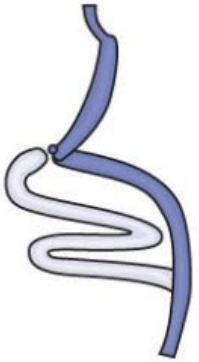
The electrooculogram, electromyogram and electroencephalogram are the core of polysomnography, the current gold standard for objective sleep monitoring. The polysomnography also includes devices such as a nasal pressure transducer and an oronasal thermistor to measure airflow parameters, pulse oximetry to assess oxygen desaturation, respiratory inductance plethysmography belts to measure abdominal and thoracic respiratory efforts, and sensors or video recording to monitor body position.[53,54] The American Academy of Sleep Medicine published a guidebook containing the rules, terminology, technical specifications and scoring guidelines for polysomnography. [55] Polysomnography is often ordered for diagnosing or treating patients with sleep-related breathing disorders, and sometimes also for suspicion of parasomnia and periodic limb movements; but not for other disorders such as insomnia or restless leg syndrome.[53]

At a glance, sleep seems to be a wasteful act, as we are incapable of doing any activities during the process, and it may even make us more vulnerable to predation. [52] However, sleep is important for our survival. Other than its rather obvious benefit of energy conservation,[52] sleep is also known to be associated with:

- Memory consolidation and brain plasticity
  Sleep plays an essential role in memory consolidation, the process of transforming labile (short-term) memories to more permanent, stable memories (long-term memories); different stages of sleep contribute to different parts of the process. Sleep is also known to contribute to neural plasticity, the ability of the brain to adapt to (internal or external) environmental changes by changing its structure and/or function. Previous studies have shown that poor sleep is associated with impaired memory and learning capacity.[56,57]
- Host defense
  When our immune system is challenged (e.g. infection), it releases a series of cytokines to initiate an acute phase response, to alert the host that the body has been infected or injured. Some of these cytokines (IL-1b, TNF-a and IL-6), induce sleepiness; which is the reason why we feel sleepy when we are sick. As the infection progresses, NREM sleep time will increase and REM sleep time, decrease.[58]

  There are some indications that the immune system can be weakened or altered with sleep deprivation but findings thus far are not strong (they are often confounded by other factors such as stress). No study has assessed how sleep influences recovery from infection (despite the common advice for patients to 'rest well' during sickness).[58]

Table 3. The most common types of bariatric surgery identified by the American Society in Metabolic and Bariatric Surgery: a summary description of the procedure, advantages and disadvantages for each type of surgical procedure.

	Gastric bypass	Sleeve gastrectomy	Adjustable gastric Band	Biliopancreatic diversion with duodenal switch gastric bypass
Procedure				
	A (top) portion of the stomach is dissected from the rest of the stomach to form a small pouch, which is then directly linked to a later part of the small intestine. This approach is considered the 'gold standard' of bariatric surgery	Approximately 80% of the stomach is removed through this procedure, leaving a slim banana-shaped stomach pouch.	An inflatable band is installed around the stomach (near the upper end), dividing the stomach into a smaller and larger portion, with a 'passage' between the two. The size of the opening of the 'passage' can be 'adjusted' by filling in sterile saline solution into the band, injected through a subcutaneous skin port.	A large portion of the stomach is removed (as in sleeve gastrectomy) and then linked to a later portion of the small intestine (as in gastric bypass but here, more of the small intestine is bypassed).

Advantages	Produces 60% to 80% excess weight loss in the long term Restricts amount of food intake May cause increase energy expenditure May cause alteration in gut hormones, that favours weight loss (increased satiety, decreased appetite) Good long-term weight loss maintenance (>50% excess weight loss)	Restricts food-storing capacity of the stomach Produces rapid and substantial weight loss, with good long-term maintenance, similar to Roux-en-Y gastric bypass A simpler procedure compared to adjustable gastric band or Roux-en-Y gastric bypass as it does not involve installing foreign objects or rerouting of the digestive tract Short hospital recovery stay (+/- 2 days) May cause alteration in gut hormones, that favours weight loss (increased satiety, decreased appetite)	Restricts food-storing capacity of the stomach Produces 40-50% excess weight loss Does not involve dissecting the stomach or rerouting the digestive tract Short hospital recovery stay (<24 hours or same day release) It is a reversible procedure Lowest risk of complications and mortality Lowest risk of vitamin/mineral deficiencies	Produces more weight loss compared to the other three procedures at five years post-surgery (60%-70% excess weight loss) Patients may eventually eat near-“normal” food Fat absorption is reduced by 70% or more May cause alteration in gut hormones, that favours weight loss (increased satiety, decreased appetite) Shown to be the most effective for diabetes, compared to the other three procedures
Disadavantages	Involves a more complex procedure than adjust gastric banding or sleeve gastrectomy, with higher risk of complications	The procedure cannot be reversed May cause long-term vitamin deficiencies	Weight loss may take more time to occur, and at a slower rate More people losing less than 50% excess weight compared to other procedures	Highest risk of complication and mortality compared to the other three procedures Longer hospital recovery stay, compared to adjustable gastric banding or sleeve gastrectomy

	May lead to vitamin/mineral deficiencies, most commonly vitamin B12, iron, calcium, and folate Longer hospital stay for post-surgical recovery compared to adjustable gastric band Need to comply with follow-up requirements, dietary recommendation and life-long vitamin/mineral supplementation	Higher risk of complication compared to adjustable gastric band	Involves installing a foreign object into the body In some instances, band slippage or erosion into the stomach as well as some other mechanical problems of the band/port/tube may occur Esophagus may dilate if patient overeats Need to comply with postoperative diet guideline and follow-up visits Highest likelihood of getting a re-operation.	More likely to cause protein deficiencies, and long-term vitamin/mineral deficiencies Need to strictly comply with follow-up requirements, dietary and vitamin/mineral supplementation guidelines

Text source: The American Society in Metabolic and Bariatric Surgery learning center webpage. Bariatric surgery procedures. Available from: https://asmbs.org/patients/bariatric-surgery-procedures, accessed December 2016.

Illustrations source: First Baptist Medical Center webpage. Bariatric Surgery for Severe Obesity. Available from https://www.fbmcdallas.com/bariatric-surgery-for-severe-obesity, accessed 13 March 2017, with permission from the creator of the illustrations, Walter Pories, M.D., FAC

Sleep Stage Classification (Old)	Sleep Stage Classification (New)	% Time Asleep	Frequency Hz (cycles per second)	Amplitude μV (microvolts)	EEG Wave Type
Awake	Wake	N/A	>12	<30	beta
Relaxed		N/A	8 - 12	<50	alpha
Non-REM Stage 1	N1	5%	4 - 8	50 - 100	theta
Non-REM Stage 2	N2	45%	4 - 8	50 - 150	theta, spindles, K-complexes
Non-REM Stage 3	N3 Delta or Slow Wave Sleep (SWS)	12%	2 - 4	100 - 150	delta & theta
Non-REM Stage 4		13%	0.5 - 2	100 - 200	delta & theta
REM	REM	25%	> 12	<30	beta

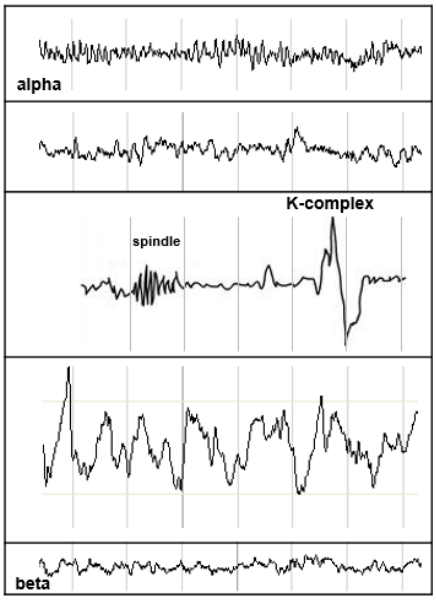


Figure 3. A summary of the electroencephalogram findings from different stages of sleep

Taken from Lockley SW, Foster RG. SLEEP: A Very Short Introduction. Oxford: Oxford University Press; 2012 [52], with permission from rightsholder, Steven W.Lockley and Russell G. Foster

- Endocrine and metabolic function
  Sleep affects the circadian rhythm (our internal 24-hour body clock), which in turn influences the hypothalamic-pituitary axis activity, carbohydrate metabolism, appetite regulation, and the hormonal control for blood pressure and body-fluid balance. Sleep disturbance has been associated with various endocrine and metabolic disorders, such as obesity and diabetes.[59]

It is believed that there may be more benefits of sleep that we have yet discovered.

2.2.2. Sleep disorders

The third (latest) edition of the international classification of sleep disorders (ICSD-3), divided sleep disorders into six major categories: insomnia, sleep-related breathing disorders, circadian rhythm sleep-wake disorders, parasomnias, sleep-related movement disorders, and central disorders of hypersomnolence. [60,61]

Insomnia, characterised by the difficulty of initiating and/or maintaining sleep,[62] is the most common type of sleep disorder. [63] The disorder usually starts to develop in adulthood.[62] It was estimated that around 10% adults in the general population has chronic or long-term (3 months) insomnia and around 30% acute or short-term.[62] This binary classification of insomnia into acute and chronic state is new in ICSD-3. Previously identified types of (primary) insomnia may still be helpful for diagnosis in a clinical setting; this includes: psychophysiologic insomnia (excessive concern over perceived inability to fall asleep), paradoxical insomnia (or “sleep state misperception”, where

patients complained of difficulty sleeping that is not supported by results from objective assessment), idiopathic insomnia (long term insomnia, starting gradually from childhood and accumulates) and behavioural insomnia of childhood (involves poor sleep behaviour during childhood, such as refusal to sleep on a regular time, reliance on inappropriate pre-sleep rituals or poor sleep environment). Insomnia may also occur as a result of a medical condition, use of certain types of drugs or substances, and presence of a mental disorder; these types of insomnia were known as "secondary insomnia" in previous version of the ICSD.[61]

Sleep-related breathing disoders include obstructive sleep apnea, central sleep apnea, and sleep-related hypoventilation/hypoxemia syndrome.[61] Obstructive sleep apnea, often encountered in individuals with obesity,[64] refers to the cessation or difficulty of breathing during sleep, due to obstructions of the upper airway, often accompanied by heavy snoring.[61] To be diagnosed with sleep apnea, there must be a total of more than 15 events (per hour) of apnea (complete cessation of breathing) or hypopnea (reduced breathing due to partial obstruction of airway), or arousal (due to increased respiratory efforts) measured through an overnight polysomnography test. Diagnosis of sleep apnea can also be established when there are 5 or more events per hour, and at least one of the following signs or symptoms: snoring, observed breathing pauses, excessive daytime sleepiness, and insomnia. Central sleep apnea also refers to partial or full cessation of breathing during sleep, but is due to reduced or absent respiratory effort instead of obstruction of the airways. In central sleep apnea, apneas/hypopneas appear in intermittent or cyclical fashion. It is also possible to have a mixture of obstructive and central sleep apnea. Sleep-related hypoventilation/hypoxemia syndrome involves hypoventilation or hypoxemia during sleep, respectively. The two are now considered separate diagnoses in the latest version of ICSD. There are six different types of sleep-related hypoventilation, one of which is obesity hypoventilation syndrome. To be diagnosed with obesity hypoventilation syndrome, there needs to be evidence of both hypoventilation (abnormally slow breathing, shown by elevated blood CO_2 level) during sleep and hypercapnia (elevated blood CO_2 level) at daytime.[61]

Circadian rhythm sleep-wake disorders take place when the circadian rhythm (our internal body clock) is out of sync with the socially-acceptable schedule pattern (external "clock"), also known as social jet-lag.[61,65] This often results in symptoms of insomnia and excessive daytime sleepiness. The delayed sleep phase disorder is one example. When allowed to have their own free schedule, people with delayed sleep phase disorder goes to bed later at night and wake up later in the following day, but have normal sleep duration, quality and pattern. This is more commonly found in children or younger adults. In advanced sleep phase disorder, the opposite happens, people go to bed earlier, and wake up earlier; this is more commonly found in elderly. In the irregular sleep-wake rhythm disorder, the 24-hour circadian rhythm is lost or impaired. This typically happens to people suffering from total blindness or institutionalised patients, who have limited exposure to natural light, opportunity to do physical activity, and factors which help sync the internal clock with the external clock. Shift-worker disorder happens to workers with unconventional (e.g. night-shitft) or irregular work hours. A sleep log, recording irregular sleep hours, is needed for this diagnosis, on top of the symptoms of insomnia and excessive daytime sleepiness commonly found in circadian rhythm sleep-wake disorders. Jet-lag disorder is an acute condition that happens after travelling across multiple timezones; the condition is usually worsened with higher number of time-zones crossed and also affected by direction of travel (generally worse eastward). [61]

Parasomnia includes a range of sleep disorders that can cause abnormal behaviours and/or experiences when entering, or during, or upon arousal from, sleep. Abnormal behaviour may involve motor movements, which are more complex in nature than that observed in sleep-related movement disorders. Unpleasant experiences may involve nightmares, sleep terrors, sleep-related hallucinations, or exploding head syndrome. Parasomnia is often found together with other sleep disorders, such as obstructive sleep apnea, and sometimes a person can have several different types of parasomnias at once. Some commonly heard parasomnia disoders include sleepwalking, sleep terrors, sleep-related eating disorder, nighmare disorder and reccurent isolated sleep paralysis. People with sleep-related eating disorder experiences episodes of eating and/or drinking of unusual or indebile substances during partial arousals from sleep. They may be injured during the process (e.g. if they attempt to cook), or suffer from health consequences (depending on the substance they ingested), but often cannot (fully) remember their experience.[61]

Sleep-related movement disorders include disorders that cause simple, stereotyped (and sometimes repetitive) movements during sleep, such as restless leg syndrome and periodic limb movement. Restless leg syndrome involves an almost irresistible urge to move one's leg, which occurs mostly in the evening or night. Painful or uncomfortable sensations often occur, which are worse at rest, and can be temporarily relieved during movements. Periodic limb movement disorder involves repetitive, stereotyped limb movements during sleep. The movements must be substantial enough to disturb sleep or cause excessive daytime sleepiness to meet the diagnostic criteria of periodic limb movements.[61]

Central disorders of hypersomnolence is discussed in the context of excessive daytime sleepiness in subsection 2.2.2.1 below.

Sleep disorders that do not fall under any of the aforementioned six main categories of sleep disorders, are classified under the "other sleep disoders" category. The supplemental category, "sleep-related medical and neurologic disorders", includes disorders that are associated with sleep, but not in themselves, sleep-disorders. For example, fatal familial insomnia (prion induced disorder that causes insomnia and other conditions, leading to death), sleep-related epilepsy, and sleep-related headaches.[61]

2.2.2.1 Excessive daytime sleepiness

Excessive daytime sleepiness (EDS) or hypersomnia is a condition of increased likelihood of falling asleep when one's intention is to remain awake. "Daytime" in "excessive daytime sleepiness" is a misnomer because depending on the "intention to remain awake", someone (e.g. shift-worker) may have sleepiness at night but still being recognised as having excessive "daytime" sleepiness. It is important to distinguish EDS from closely related phenomena such as fatigue/tiredness (mental/physical exhaustion that can be resolved with rest, but not necessarily sleep) and anhedonia (a general lack of interest to be involved in any activities, where sleep is simply a resulting behavioural manifestation).[66-69] A wide range of sleep disorders, such as obstructive sleep apnea, insomnia and circadian rhythm sleep wake disorders, produce EDS as a symptom (see section 2.2.1).[61]

Causes of EDS that are independent of any sleep disorders, are categorised under one major group in ICSD-3, "central disoders of hypersomnolence".[60,61] This includes EDS that results from medical conditions (other than sleep disorders), use of certain drugs or substances (e.g. hypnotics, antidepressants), and psychiatric disorders. Voluntary sleep restrictions (insufficient sleep syndrome) due to social demands or any other reasons, also result in EDS, but may resolve with extended sleep.[61] EDS is also the primary symptom of narcolepsy and Kleine-Levin syndrome, which are relatively rare in the general population.[70] Narcolepsy may occur with or without cataplexy (sudden, involuntary, muscle weakness or paralysis) depending on the type (type 1 or 2), and can be diagnosed through multiple sleep latency test (coupled with overnight polysomnography) and hypocretin test. Kleine-Levin syndrome involves days to weeks of recurrent hypersomnia, accompanied with any combination of eating disorder, unrestratined (sexual) behaviour, cognitive dysfunction and perceptual disturbance.[61,70]

When EDS occurs in a healthy individual with normal sleep time and patterns, the possibility of longer sleep requirement needs to be considered. Some individuals require a longer duration of sleep than average people (general cut-off is 10 hours, but may be more, depending on age); when the need is not met, EDS results.[61]

EDS that did not result from any of the conditions listed above is known as idiopathic hypersomnia.[61]

EDS may be assessed objectively or subjectively (The maintenance of wakefulness test is similar to the multiple sleep latency test but the examinee is asked to stay awake instead of falling asleep, in a similarly sleep-condusive environment, for 40 minutes at a time. The examinee maintains a sitting position (head and back partially supported by pillows), instead of a sleeping position, but similarly on a bed. If the examinee remains awake during the entire 40 minutes, the sleep latency is assumed to be 40 minutes for that particular test round.[67,70]). The most commonly used objective measures are the multiple sleep latency test and maintenance of wakefulness test. The multiple sleep latency test involves asking the examinee to take a series of naps (usually 4 to 5 naps) with two hour intervals, in a sleep-condusive environment (low temperature, dim/no light). In each nap, the examinee is given 20 minutes to fall asleep, and sleep latency (the time it takes for the examinee to fall asleep upon initiation of the test) is measured in each attempt to nap. As in polysomnography, electroencephalogram, electromyogram and electrocardiogram are also used to monitor sleep in a multiple sleep latency test. If the examinee cannot fall asleep within 20 minutes, a sleep latency of 20 minutes is assumed for that particular attempt. As a general rule, EDS is defined as an average sleep latency of 8 minutes or less. The multiple sleep latency test needs to be preceeded by an overnight polysomnography, to ensure good quality sleep in the night prior to the examination, and urine drug screening to eliminate the possibility of pharmacological influence on the test result. It is also recommended that the examinee maintains two weeks of regular sleep prior to the test, which can be tracked through sleep diaries or actigraphy. The multiple sleep latency test has a weakness of measuring EDS at one particular day, under the same condition. It is assumed that the average sleep latency measured through the multiple sleep latency test accurately reflects EDS in conditions other than the setting of multiple sleep latency test, and that there is little or no day-to-day variation. The multiple sleep latency test is also expensive to perform, and requires the presence of a sleep technician. Despite these limitations, the multiple sleep latency test remains the best option for diagnosing narcolepsy (detection of sleep-onset REM period),

for comparing drug efficacy on sleepiness, and for comparing different tools to measure sleepiness under the same conditions.[53,68]

The maintenance of wakefulness test is similar to the multiple sleep latency test but the examinee is asked to stay awake instead of falling asleep, in a similarly sleep-condusive environment, for 40 minutes at a time. The examinee maintains a sitting position (head and back partially supported by pillows), instead of a sleeping position, but similarly on a bed. If the examinee remains awake during the entire 40 minutes, the sleep latency is assumed to be 40 minutes for that particular test round.[68,71] Interpretation of average sleep latency from the maintenance of wakefulness test is less straightforward than that from the multiple sleep latency test.[68,71] An average sleep latency of less than 8 minutes is similarly considered abnormal, but to indicate alertness, a higher cut-off is needed. Data from presumably normal study populations showed a mean average sleep latency of 30.4 minutes, with upper 95% confidence interval of 40 minutes (maximum value, the expected value in practise).[71,72] The interpretation of the average sleep latency from maintenance of wakefulness test needs to be accompanied with clinical judgment. The average sleep latency measured in multiple sleep latency test and maintenance of wakefulness test will somewhat differ. In the maintenance of wakefulness test, the light input from opened eyes and the maintenance of sitting posture may keep the examinee awake for longer time, hence producing higher average sleep latency test. Some examinees fall asleep faster during the maintenance of wakefulness test than the multiple sleep latency test, perhaps attributable to “paradoxical intention”, from the fear of failing the test. Where the multiple sleep latency test is usually used for diagnostic purpose, the maintenance of wakefulness test is usually used to test a patient’s response to treatment.[68,71]

Table 4. Methods of measuring daytime sleepiness

Objective	Multiple sleep latency test
	Maintenance of wakefulness test
	Osler test
	EEG and EOG
	Psychomotor Vigilance Test
	Video camera methods for detecting eyelid closure - PERCLOS
Subjective	Epworth Sleepiness Scale
	Karolinska Sleepiness Scale
	Stanford Sleepiness Scale
	Visual analogue scale
	Sleep-wake activity inventory
	One-/two-point questions

Source: Johns MW, 2009.[68]

The most commonly used tool to measure subjective sleepiness is the Epworth Sleepiness Scale (ESS).[53,73] It is a self-administed questionnaire, consisting of eight commonly

encountered daily activities (**Figure 4**). Each situation needs to be rated from 0 to 3, with the increasing likelihood of falling asleep, which gives an overall score that ranges from 0 to 24. EDS is defined as ESS scores>10.[68,73] The ESS has been shown to have moderate correlation with the Multiple Sleep Latency test[73,74] and has high individual test-retest reliability.[75] ESS requires the responder to reflect on their sleepiness level "in recent times", to minimize day-to-day variations.[68,73] Other commonly used questionnaires are the Karolinska Sleepiness Scale and the Stanford Sleepiness Scale, both of which measures daytime sleepiness at one moment in time. The responders rate their level of sleepiness in a seven- (Stanford) or nine- (Karolinska) point scale.[53,68] It is important to note that, as in any other subjective measurements, the validity of these questionnaires depends strongly on the responder's perception, mood and education level. However, considering practicality, cost-effectiveness, and time-efficiency; questionnaires (particularly the ESS) remain the preferred option in large-scale population studies and also in clinics for screening puposes.[53,68]

Epworth Sleepiness Scale

Name: _____Today's date: _____

Your age (Yrs): _____ Your sex (Male = M, Female = F): _____

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired?

This refers to your usual way of life in recent times.

Even if you haven't done some of these things recently try to work out how they would have affected you.

Use the following scale to choose the **most appropriate number** for each situation:

0 = would **never** doze
1 = **slight chance** of dozing
2 = **moderate chance** of dozing
3 = **high chance** of dozing

It is important that you answer each question as best you can.

Situation	Chance of Dozing (0-3)
Sitting and reading	___
Watching TV	___
Sitting, inactive in a public place (e.g. a theatre or a meeting)	___
As a passenger in a car for an hour without a break	___
Lying down to rest in the afternoon when circumstances permit	___
Sitting and talking to someone	___
Sitting quietly after a lunch without alcohol	___
In a car, while stopped for a few minutes in the traffic	___

THANK YOU FOR YOUR COOPERATION
©M.W. Johns 1990-97

Figure 4. the Epworth Sleepiness Scale

Taken from Johns MW. Chapter 2 - What is excessive daytime sleepiness? In: Fulke P, Vaughan S, editors. Sleep Deprivation: Causes, Effects and Treatment: Nova Science Publishers; 2009, page 10, [68] with permission from right holder, Nova Science Publishers, Inc.

Original version of the questionnaire was published in Johns MW, 1991[73]

2.2.3. Consequences and significance

A wide range of sleep disorders produce EDS as a symptom, which in turn has been associated with health conditions such as depression and diabetes, risk factors such as reduced exercise or physical activity,[76] and consequences such as accidents,[77,78] injuries,[79] and reduced academic/professional performances.[80-82] EDS has also been associated with increased likelihood of developing disability,[83,84] and (inconsistently) with increased risk of mortality.[85-88] EDS is especially important for certain subgroups of the population, for example truck/bus drivers,[89] physicians,[90] and judges;[81] whose occupations substantially influence public safety. It was estimated that up to 1 in 3 people in the general American population experience EDS.[91]

Sleep deprivation that occurs with most sleep disorders, may disturb the functions of sleep (see subsection 2.2.1), resulting in conditions such as memory impairment,[56] endocrine and metabolic disorders,[59,92] cardiovascular disease,[93,94] and poor mental health.[95,96] It was estimated that in 2014, approximately 35% of American adults did not get sufficient sleep (less than 7 hours).[97]

The importance of sleep health is becoming increasingly recognised; perhaps due to the growing prevalence of sleep problems[98] and its observed consequences.[99,100] More rigorous study on the identification of potential causes and consequences of sleep problems is necessary to help build better prevention strategies and to provide further understanding on the extent to which poor sleep is an important health problem.

2.2.4. Prevention

To avoid having or exacerbating existing sleep poblems, one can start from adopting good sleep habits, also often known as good sleep hygiene.[101,102] These seemingly logical and simple guidelines are often neglected, especially with the advancement of technology (blue-light emitting devices[103,104]) and increasing demand from work. Guidelines on sleep hygiene are provided by various sleep health associations, organizations or foundations, delivering similar main messages, which are summarised below.[101,102]

- Try to maintain consistent sleep-wake schedule throughout the week
- Try to create and maintain a pleasant and relaxing environment to sleep in (comfortable bed, good temperature, minimum light, free from distractions)
- Try to associate your bed with sleep, by not doing other activities such as watching TV or reading books on the bed.
- Try to do only relaxing activities before bed, and make it a routine. Avoid emotional conversations and do not think about or deal with your problems during bed-time.
- Exposure to sunlight during the day can help promote sleep at night.
- Vigorous exercise in the morning or late afternoon, and/or relaxing exercise such as yoga close to bedtime may help promote a good night sleep.
- Time your meal appropriately, not too close but also not too far from bedtime. Going to bed too full or too hungry, disturbs sleep. Spicy food are not ideal for those with sleep problems.
- Avoid taking naps during the day, especially during the evening.
- Avoid taking caffeinated drinks or food and other stimulants, close to bed time (approx. 4 hours). Chocolate contains caffeine.

- Avoid alcohol. Although alcohol induces sleep, it will also induce arousal during its metabolism.
- Leave the bedroom after 20 minutes of unsuccessful attempt to sleep; return when you are tired.
- There are separate, more detailed guidelines regarding use of technology, but the general guideline is to avoid exposure to blue light from devices such as televisions, computers and smart phones, approximately one hour before bed-time. If this is not possible, some mobile applications can be downloaded to reduce the emission of blue light.[104]

The required amount of sleep decreases with age, this is reflected in the guideline from the National Sleep Foundation in **Figure 5**. The guideline applies for a majority of the population, but note that some people may require less or more amount of sleep, to allow proper daytime functioning.

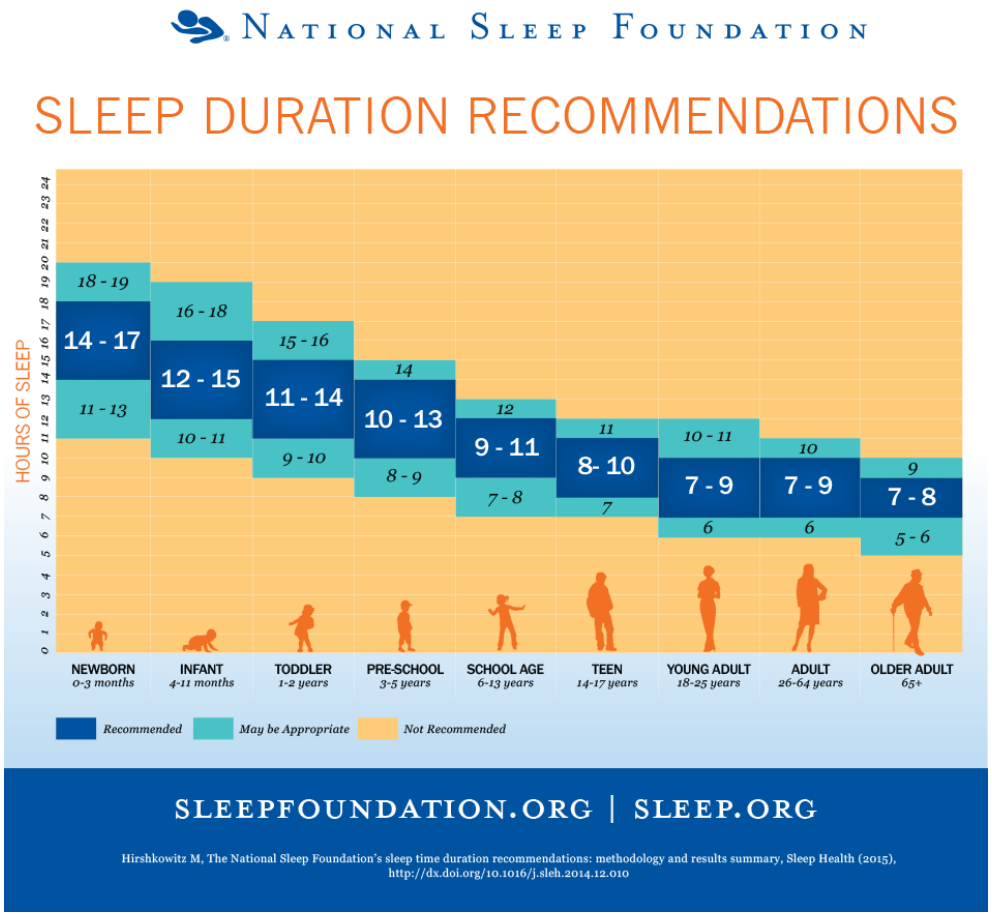


Figure 5. The recommended hours of sleep by age groups

Taken from the National Sleep Foundation. How much sleep do we really need? 2015; Available from: https://sleepfoundation.org/how-sleep-works/how-much-sleep-do-we-really-need[105], with permission from rightsholder, National Sleep Foudnation.

The figure was created based on findings form Hirshkowitz M, et al.[106]

> *"Sleep and watchfulness, both of them, when immoderate, constitute disease."*
>
> *-Hippocrates*

Maintaining sleep hygiene and getting sufficient duration of sleep can be a challenge in the face of longer work hours and greater entertainment options in today's society. However, it is important to remember that sleep health is essential for our safety, health and well-being in the long term.[100]

2.2.5. Treatment

Treatment options differ with different sleep disorders. For example, for insomnia, psychological-behavioural treatment such as cognitive behavioural therapy is preferable to pharmacological treatment through hypnotics/sedatives, which can lead to unwanted side effects.[63,107] The primary treatment option for obstructive sleep apnea is continuous positive airway pressure, although depending on the situations, other treatment options such as mandibular advancement oral appliance therapy, nasal expiratory positive pressure, positional therapy, weight loss, electrical stimulation of the hypoglossal nerve or even upper airway surgeries (nasal septoplasty, uvulopalatopharyngoplasty, tonsillectomy, tongue advancement procedures and maxillomandibular advancement surgery) may also be considered.[108,109] For shift-worker disorder, when worker has no control over shift-work scheduling, circadian intervention that involves bright light with or without exogenous melatonin is recommended. Melatonin or hypnotics are also sometimes used to improve daytime sleep, and napping with or without caffeine or modafinil/armodafinil to improve night-time alertness.[110] For restless leg syndrome, primary treatment options include calcium channel α2∂ ligand, dopamine agonists, and dopamine precursors. Hypnotics/sedatives are sometimes used to promote sleep continuity in those with restless leg syndrome.[111]

Treatment for EDS involves treating its underlying cause.[112] For example, continuous positive airway pressure has been shown to improve daytime sleepiness in people with obstructive sleep apnea.[112-114] Wake-promoting agents such as modafinil, armodafinil, and amphetamines can also be used to manage EDS in some circumstances.[112,115]

In this section, treatment strategies that are relevant to the studies included in this thesis, will be discussed in further detail.

2.2.5.1. Continuous positive airway pressure

The main problem in obstructive sleep apnea patients is the collapse of the upper airway during sleep, obstructing airflow. In 1981, Sullivan et al introduced the idea of using continuous positive airway pressure to treat obstructive sleep apnea.[116] The device applies air pressure to the upper airway (usually through a nasal mask), that works as a pneumatic splint, to keep the upper airway opened during sleep (**Figure 6**).

The minimum magnitude of pressure required to keep the airway open, varies throughout the stages of sleep and is different for different individuals. The patients are usually prescribed with a fixed, optimal level of pressure, manually titrated by a sleep technician during full-night polysomnography. The optimal pressure is the pressure that can eliminate all apneas, hypopneas, arousals, and snorings during all stages of sleep, at all sleep positions (REM sleep at supine position requires the highest pressure); and at the same time keep the oxygen saturation above 90%, as well as minimise air leak through the continuous positive airway pressure mask. The titration session is usually

separate to the initial diagnostic polysomnography session; but the two sessions can be combined (split-night polysomnography) if the diagnosis of obstructive sleep apnea becomes obvious during the first two hours of polysomnography (≥40 events/hour).[117]

An alternative to continuous positive airway pressure, which requires manual titration, is the auto-titrating positive airway pressure. The auto-titrating positive airway pressure device is equipped with the capacity to continuously detect changes in airflow and resistance of the upper airway throughout the sleep stages, and adjust its pressure accordingly, in real time.[109,117] Two meta-analysis comparing continuous and auto-titrating positive airway pressure seems to prefer the latter, for slight improvement in compliance, sleep architecture and some outcome measures (daytime sleepiness, oxygen saturation).[109,118,119] The patients also seemed to prefer auto-titrating, rather than continuous positive airway pressure. [109,118]

Positive airway pressure therapy is usually prescribed for those with moderate or severe obstructive sleep apnea (≥15 apneas/hypopneas per hour); and also for those with mild obstructive sleep apnea (5-14 apneas/hypopneas per hour) but with comorbidities.[117] Despite the apparent benefits of positive airway pressure on obstructive sleep apnea, the compliance rate remains quite low (30-60%).[109] Several factors known to affect compliance include: cost of device, poor mask fit, claustrophobia, lack of motivation, nasal congestion, skin irritation, etc.[109,117] Interventions involving education, supportive care, as well as behavioural therapies, have been shown to be effective in improving general compliance. For patients with nasal congestion, heated humidification helps. Patients not liking the nasal mask may opt for other options, such as the full-face mask, the nasal pillows, or the oral interfaces. Hypnotics such as eszopiclone are sometimes prescribed to improve sleep in patients using positive airway pressure because patients often complain about disturbed sleep or difficulty in falling asleep during the early days or weeks of positive airway pressure treatment initiation. Although there is no evidence for adverse effects, the use of hypnotics in those with obstructive sleep apnea should always be approached with caution.[117]

2.2.5.2. Sleep-promoting medications

Prescribing pharmacological treatment to sleep disorders are less preferred in the presence of other non-pharmacological options, because they have been associated with increased risk of vehicle accidents,[120] fall-related injuries,[121] cognitive decline[122] and mortality.[123] However, pharmacological treatments are still essential for some patients; either as the primary treatment, or as a complement to non-pharmacological treatments.[107]

Under the World Health Organization's Anatomical therapeutic chemical classification system,[124] medications with the primary indication for promoting sleep are grouped under pharmacological subgroup "hypnotics and sedatives", coded as N05C. Commonly used hypnotics and sedatives include benzodiazepines, benzodiazepine-related drugs (also known as nonbenzodiazepines or the "Z-drugs"), and more recently, metalonin-receptor agonists (**Table 5**).[124-126] Other older chemical subgroups such as barbiturates and aldehydes are less commonly used.[125,126]

The gamma-aminobutyric acid-A receptor ($GABA_A$), which functions as a chloride ion channel, plays a central role in the pharmacology of hypnotics and sedatives. The main inhibitory neurotransmitter in our central nervous system, GABA, binds to the $GABA_A$ receptor, allowing the influx of chloride ions, which hyperpolarizes the neuronal membrane and prevents the occurrence of action potentials in the neuron. Benzodiazepines, benzodiazepines-related drugs, barbiturates, and many other hypnotics and sedatives, bind to different molecular sites or components of $GABA_A$ receptor as agonists, producing similar net influx of negatively charged chloride ions.[125,126]

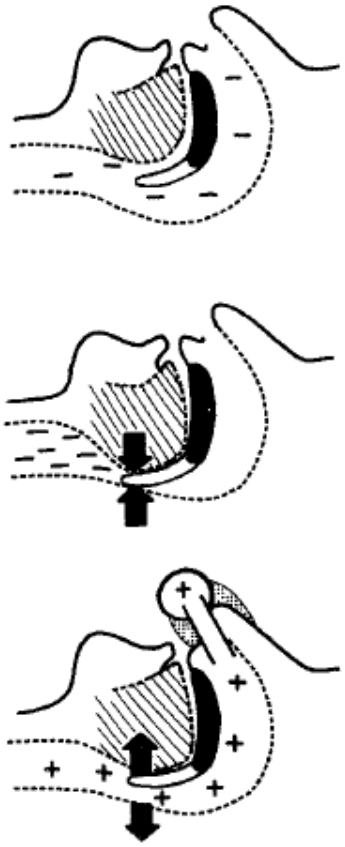


Figure 6. Continuous positive airway pressure

The upper panel shows the upper airway when the individual is awake, the middle panel, when the individual is asleep (collapse airway due to loss of muscle tone), and the lower panel, when the lower figure when the continuous positive airway pressure is applied through the nose (forces opening of the collapsed airway).

Taken from Sullivan CE, Issa FG, Berthon-Jones M, Eves L. Reversal of obstructive sleep apnoea by continuous positive airway pressure applied through the nares. Lancet. 1981 Apr 18;1(8225):862-5,[116] with permission from rights holder, *Elsevier*.

The $GABA_A$ receptor consists of five molecular subunits, from any of the polypeptide classes α, β, γ, δ, ε, π, etc. About 40% of $GABA_A$ receptors have the combination of α-1, β-2, and γ-2 subunits; and perhaps about 20% have the combination of α-3, β-2, and γ-2 subunits. Most benzodiazepines bind to all types of $GABA_A$ receptors, but the newer benzodiazepines-related drugs more selectively binds only to those receptors with α-1 subunits. This can perhaps explain why benzodiazepines produce wider effects unrelated to sleep, compared to benzodiazepines-related drugs, such as memory impairment, anti-anxiety and muscle-relaxing effect. Benzodiazepines and benzodiazepines-related drugs have different chemical structures and have different affinities to molecular components of $GABA_A$ receptors; but their mechanism of actions are quite similar.[125,126] There is evidence suggesting that benzodiazepines-related drugs produce fewer side effects and present less risk of dependence and misuse, compared to benzodiazepines.[125,127]

Table 5. A list of benzodiazepines, benzodiazepine-related drugs, and melatonin receptor agonists listed under pharmacological subgroup "hypnotics and sedatives" in the World Health Organization's Anatomical therapeutic chemical classification system.

WHO ATC code	Chemical subgroup/ Chemical substance
N05CD	**Benzodiazepines derivatives**
N05CD01	Flurazepam
N05CD02	Nitrazepam
N05CD03	Flunitrazepam
N05CD04	Estazolam
N05CD05	Triazolam
N05CD06	Lormetazepam
N05CD07	Temazepam
N05CD08	Midazolam
N05CD09	Brotizolam
N05CD10	Quazepam
N05CD11	Loprazolam
N05CD12	Doxefazepam
N05CD13	Cinolazepam
N05CF	**Benzodizepines related drugs**
N05CF01	Zopiclone
N05CF02	Zolpidem
N05CF03	Zaleplon
N05CF04	Eszopiclone
N05CH	**Melatonin receptor agonists**
N05CH01	Melatonin
N05CH02	Ramelteon
N05CH03	Tasimelteon

Source: The World Health Organization's Anatomical therapeutic chemical classification system[124]

Melatonin, derived from serotonin, is a hormone produced by the pineal gland in the central nervous system that correlates strongly with sleep propensity. The release of melatonin is rhythmic and controlled by the suprachiasmatic nuclei, the central body "clock" in our brain that regulates the circadian rhythm. The release of melatonin is heavily influenced by the presence/absence of light, with greater release at nightime (usually starts to increase at 9 pm, and lasts until 4 am) than during the day. The mechanism through which melatonin promotes sleep is unclear; but is perhaps related to its binding to the melatonin-1 and melatonin-2 receptors in the suprachiasmatic nuclei, as a feedback mechanism to regulate the circadian rhythm. Melatonin receptor agonists mimics the role of melatonin. Melatonin (receptor agonists) have no known direct effect to $GABA_A$ receptors. Despite incomplete understanding on how melatonin works in promoting sleep, melatonin receptor agonists are now commonly used to treat sleep problems, especially those related to circadian rhythm sleep-wake disorders, where they are more effective. The timing of melatonin intake plays a crucial role in determining success of the treatment; it needs to be directed with good knowledge of the timing of the circadian rhythm. Unlike benzodiazepines and benzodiazepines-related drugs, use of melatonin is not associated with problems of tolerance and dependence.[107,125,128-130]

The choice of hypnotics and sedatives depends on patient's response to treatment, because there is a wide person-to-person variability in terms of responsiveness to treatment using a particular drug in the same family.[107] The decision on which drug to use also depends on the overall clinical presentation of the patient. For example, in patients with high risk of substance abuse, propiomazine, which has not been associated with dependence,[131] may be preferable to benzodiazepines. The use of benzodiazepines and benzodiazepines-related drugs are usually contraindicated in those with obstructive sleep apnea, due to fear of upper airway muscle relaxation and prolongation of apnea; however recent studies showed that zopiclone may be safe and beneficial to use in those with sleep-disordered breathing.[132,133]

Other medications which primary indications are not for sleep problems, are also often used to treat sleep problems. This includes antihistamines (older generations, e.g. hydroxyzine) and alcohol, which are easily acquired over-the-counter.[125,126] Although alcohol may induce sleep, it may disturb sleep at a later stage and there is a risk of dependence and abuse.[125] Therefore, alcohol is not recommended for use as a sleep-promoting agent. Off-label use of prescribed medications include antipsychotics (e.g. quetiapine), antidepressants (e.g. Trazodone), anxiolytics (e.g. diazepam), and antiepileptics (e.g. clonazepam).[125,126] A study on a large managed-care population in 2004 showed that antidepressants and anxiolytics were more frequently prescribed for treatment of insomnia than hypnotics.[134] This is perhaps due to the perceived worse side effects of hypnotics and sedatives (e.g. rebound insomnia, confusional arousal) compared to aforementioned classes of drugs, and concerns over the issues with tolerance and dependence. It is important to note that other classes of drugs such as antidepressants, also have their own list of side effects (weight gain, diabetes, anticholinergic side effects) and evidence supporting their effectiveness as hypnotics/sedatives are poor.[107]

2.3. Obesity and sleep

Although the relationship between obesity and sleep health can be bidirectional,[135] given the focus of this thesis, most of the narrative will focus on literature discussing obesity as a potential cause of sleep problems.

2.3.1. The relationship between obesity and sleep disorders

The oldest, most established relationship between obesity and sleep disorders is that between obesity and obstructive sleep apnea. It was estimated that approximately 70% of individuals with obstructive sleep apnea are obese.[136] Longitudinal studies consistently showed strong relationship between weight change and change in severity of obstructive sleep apnea measured through apnea-hyopnea index.[137-139] For example, through the Wisconsin Sleep Cohort Study, Peppard et al found that 10% weight gain was associated with 32% increase (more severe) apnea-hypopnea index, and 10% weight loss, with 26% improvement in apnea-hyopnea index.[137] Previous randomised controlled trials have also shown improvement in severity of obstructive sleep apnea following weight loss through dietary interventions.[140-142] Physical activity interventions aiming for weight loss, produced some improvement in severity of obstructive sleep apnea despite no-/minimum- weight loss, suggesting the possibility of the independent association between physical activity and obstructive sleep apnea.[143,144] The only randomised controlled trial comparing bariatric surgery and meal replacement therapy in treating obstructive sleep apnea, showed that the difference in the reduction of severity of obstructive sleep apnea in both groups was not statistically significant.[145] However, the sample size was relatively small (n=30 in each group). Araghi et al performed a meta-regression analysis between the amount of weight change and the degree of improvement in severity of obstructive sleep apnea; the correlation coefficient was 0.56 but with p value of 0.186.

The authors noted the possibility of low power (n=11).[146] Theoretically, obesity may cause obstructive sleep apnea through fat accumulation around the neck, which exerts mechanical pressure on the upper airway, promoting collapse of the upper airway during sleep. Also, fat accumulation around the thorax and abdomen results in reduced lung compliance and resting volume, which in turn predisposes to upper airway collapsibility through reduced tracheal caudal traction.[25,108] Independent of mechanical effects, obesity may also cause obstructive sleep apnea through other pathways such as increased level of leptin, a hormone released by adipose tissue which may reduce respiratory drive, and through the release of pro-inflammatory cytokines, which damages neuromuscular control of the upper airway.[25] It is hypothesised that obstructive sleep apnea may also cause obesity, through pathways such as increased energy expenditure from increased work of breathing, altered diversity of gut microbiota, reduced physical activity due to excessive daytime sleepiness and altered dietary consumption from sleep deprivation.[25,147,148]

Obesity has also been associated with insomnia.[135] Cross-sectional studies suggest that individuals with obesity are more likely to report symptoms of insomnia than those without.[98,149] A study using the National Health Interview survey estimated that 22.4% of obese U.S. adults in 2012 had problems with insomnia.[98] Longitudinal studies assessing the relationship between baseline obesity status and incident insomnia have produced inconsistent results,[150-153] while studies assessing weight gain and incident insomnia have produced more consistent results, supporting the role of weight gain as a risk factor for insomnia. [151,153] A randomised controlled trial of aerobic exercise in overweight or obese individuals found improved insomnia symptoms following the intervention, despite lack of substantial weight loss; again suggesting the potential benefit of exercise on sleep health, independent of weight loss.[154] No dietary or surgical weight loss interventions thus far have assessed insomnia as an outcome. The pathways through which obesity may cause insomnia have not been formally assessed, but it is likely to be due to obesity-related comorbidities such as depression, asthma, heart problems, and low back pain, which were shown to predict incident insomnia; [151-153,155] or perhaps it is the constellation of all physical disorders caused by obesity (see subsection 2.1.3) instead of any one particular medical condition.[153,155] It is also possible that obesity is a marker of an unhealthy lifestyle, which may involve poor sleep hygiene, that in turn can initiate or exacerbate insomnia. On the other hand, insomnia may also lead to obesity,[156] through hormonal changes and reduced physical activity associated with sleep deprivation (see subsection 2.1.2). There is a great amount of evidence supporting the relationship between short sleep duration and obesity,[18-20,157] but short sleep duration may not always represent insomnia; the role of voluntary sleep curtailment must be considered. Also, most hypotheses linking short sleep duration and obesity were in the direction of short sleep causing obesity.[18,19]

Another sleep disorder that may be related to obesity is restless legs syndrome.[135] Earlier studies were mostly cross-sectional and have produced inconsistent results;[158] some finding a significant association between obesity and restless legs syndrome,[159,160 161]some not.[162-164] More confidence in the relationship between obesity and restless leg syndrome was gained from a more thorough study conducted by Gao et al, which not only found a significant cross-sectional relationship of restless legs syndrome with obesity, but also of both early-adulthood obesity and subsequent weight gain, with restless leg syndrome.[165] This is further confirmed by more recent longitudinal studies assessing baseline obesity and incident restless legs syndrome.[166] The mechanism through which obesity may cause restless legs syndrome is unclear, but is hypothesised to be related to reduced dopamine metabolism in the central nervous system.[166]

Circadian-rhythm sleep-wake disorders may cause obesity, which explains the higher prevalence of obesity in shift-workers compared to normal day workers. The desynchronization of the internal

body clock and the external clock (day/night alteration) in shift workers, results in a series of events such as altered metabolism of glucose and lipid, disruption of ghrelin and leptin, etc; which predisposes to obesity.[167,168] Dietary content may influence the circadian rhythm,[167] but there is no evidence of obesity per se causing circadian-rhythm sleep-wake disorders. Given that individuals with obesity fall asleep more easily during the day (obesity-related EDS), than the night (overactivation of sympathetic nervous system), it is not impossible that obesity may lead to circadian-rhythm sleep-wake disorder.[169]

2.3.1.1. The relationship between obesity and excessive daytime sleepiness

In earlier years, the relationship between obesity and EDS was an intuitive common consensus, because EDS is recognised as one of the cardinal symptoms of obstructive sleep apnea, of which obesity is a strong risk factor. It was not until 1998, when Vgontzas et al[169] suggested the possibility of obesity-related EDS in individuals free from obstructive sleep apnea, that reseachers began to take interest in assessing the potential role of obesity in EDS, as a separate entity to obstructive sleep apnea.

Since then, cross-sectional studies have been published,[170-174] confirming the relationship between obesity and increased likelihood of having EDS (with or without taking into account obstructive sleep apnea). More recently, longitudinal studies have also shown significant relationship of baseline obesity status and of weight gain with incident EDS;[151,175,176] and of weight loss with remission of EDS.[151] A randomised controlled trial assessing the effectiveness of a 9-week weight loss intervention program through a very low energy diet, found substantial improvement in daytime sleepiness at the end of the program.[140] Another randomised controlled trial with a similar sample size (n= 37+35) and (12-week) dietary program found no significant difference in EDS improvements between the intervention and the control group,[142] potentially due to longer follow-up (1 year) and smaller magnitude of weight loss, reducing the power to detect smaller differences in change of daytime sleepiness between study groups. Sengul et al and Kline et al. did not find evidence for improved EDS following a 12-week aerobic exercise program. They also did not find reduction in measures of adiposity.[144,177] Pedometer-based weight loss studies by Morgan et al led to significant weight loss without improvement in EDS. However, the authors noted the possibility of insufficient power, due to assessment of EDS as a secondary outcome.[178,179] A pilot randomised controlled trial study by Desplan et al showed improvement in daytime sleepiness following weight loss through a combined dietary and exercise weight loss program for 4 weeks.[180] Similarly, Ng et al showed improvement in EDS immediately following a 4-month lifestyle modification program, which effect was sustained at 1-year follow-up, although the between-group significance was borderline.[181] Weight loss through medications (zonisamide, liraglutide and phentermine/topiramate combination) did not seem to affect EDS.[182-184] In the only randomised controlled trial comparing bariatric surgery (laparoscopic adjustable gastric banding, n=30) and very-low-calorie diets (n=30), severity of EDS improved in both treament groups, but the between-group difference was not significant, despite the relatively larger magnitude (almost two-fold) of improvement observed in the surgery group.[145] Note that in all of the aforementioned randomised controlled trials, EDS was assessed as a secondary outcome, which could mean that sample size calculation in these studies did not take into account the power to detect substantial difference in change in severity of EDS. There have been reviews and meta-analyses synthesising the effect of weight loss interventions on EDS, but all as a secondary aim to assessing the effect of weight loss interventions on obstructive sleep apnea,[146,185] which risks exclusion of studies that should otherwise be included into the review.

Taken together, it seems like: 1) a relatively large amount of weight loss may be needed to produce substantial improvement in daytime sleepiness, and 2) EDS only improves with weight loss up to a

certain degree, after which EDS ceases to improve (floor effect), and 3) the amount of weight loss is likely to have more effect on EDS than exercise per se. Further study is needed to confirm these hypotheses.

There are several pathways through which obesity may lead to EDS. As previously mentioned, the initial common consensus was that obesity causes EDS mainly through obstructive sleep apnea, but this was later challenged by the findings of obesity-related EDS in those without obstructive sleep apnea.[169] Panossian et al summarised the three main groups of evidence, supporting the relationship between obesity and EDS, independent of obstructive sleep apnea.[186] Firstly, in obese individuals with and without obstructive sleep apnea, the prevalence of EDS was approximately similar. Secondly, even though obesity is highly correlated with measures of obstructive sleep apnea (e.g. apnea-hypopnea index), measures of obstructive sleep apnea are only weakly correlated with measures of EDS. Finally, there is a residual level of EDS that cannot be removed with the treatment of continuous positive airway pressure for obstructive sleep apnea.[186] It is therefore, highly likely that there are other pathways linking obesity to EDS, such as through sleep disruption from overaction of the sympathetic nervous system, other sleep disorders such as insomnia, restless leg syndromes, and circadian-rhythm sleep-wake disorders (see subsection 2.3.1), or medical conditions such as diabetes and depression. Another possibility is through metabolic disruption and chronic inflammation associated with obesity. Inflammatory cytokines released by adipose tissue such as tumor necrosis factor-α and interleukin-6, may have direct influence on EDS.[186,187]

On the other hand, it is possible that EDS may lead to obesity through reduced physical activity;[25,76] or EDS as a marker of sleep deprivation, leads to irregular hormonal regulation (leptin and ghrelin), that in turn leads to obesity (see subsection 2.1.2).[20]

2.3.2. The relationship between obesity and sleep medications (hypnotics and sedatives)

Studies assessing the relationship between obesity and sleep medications have shown mixed results A study by Ohayon et al in 2002,[188] using data from a nationally representative sample in Italy in 1996-1997, did not find a significant relationship between obesity and use of sleep-promoting medications (anxiolytics, hypnotics, and antidepressants). A similar study by Marques-Vidal et al in 2006,[189] using national survey data from 1998 and 1999 in Portugal, found that obesity is associated with less use of sleep-promoting medications (anxiolytics, hypnotics and antidepressants) in men. Another study by the Counterweight Project Team in 2005, using data from several primary care centers in the United Kingdom in 2000-2002, found that drugs prescribed for the central nervous system (which includes hypnotics, sedatives and other sleep-promoting medications) were more common in those with than without obesity; also, of all individuals receiving hypnotics prescription, those with obesity were more likely to be prescribed with greater dose/ longer treatment of hypnotics than those without. A study by Vozoris et al in 2011,[190] using data from Canadian national health surveys in 2003, found that those with severe obesity (BMI≥35 kg/m^2) were more likely to use sedatives than individuals with normal weight (BMI 18.5-24.9 kg/m^2). This study included the most complete adjustment set in their analysis model, compared to the other three studies.

There are several possible explanations for the discrepancies in the study findings. Firstly, one must understand that although hypnotics and sedatives can be used to treat obesity-related sleep disorders such as insomnia, restless leg syndrome, and circadian rhythm sleep-wake disorders (see subsections 2.2.5 and 2.3.1) in people with obesity, its use is contraindicated in the presence of

obstructive sleep apnea (which is commonly found in individuals with obesity). This is because use of hypnotics and sedatives may cause the relaxation of airway muscles and prolonged episodes of apnea, further exacerbating the severity of obstructive sleep apnea. For this reason, clinicians might be more careful and conservative in prescribing hypnotics and sedatives for individuals with obesity. This may explain the finding of a lack of association between obesity and use of sleep-promoting medications by Ohayon et al;[188] and the finding of an association between lower use of sleep-promoting agents with obesity found by Marques-Vidal et al.[189] However, in more recent years, with the development of newer hypnotics and sedatives (e.g. zopiclone) with fewer side effects that may even be beneficial for use in obstructive sleep apnea, clinicians might have felt more confident in prescribing hypnotics and sedatives in individuals with obesity; explaining the finding of increased use of hypnotics and sedatives in those with obesity, from Vozoris et al. and the Counterweight Project Team.[190,191] The two-fold increase in the overall prescriptions of sedatives in Canada between 1994 and 2003, shown by Vozoris et al, further supports the hypothesis of a more relaxed attitude towards the prescriptions of hypnotics and sedatives by clinicians in later years.[190]

Another potential expalanation for the discrepancy in results is the different countries in which the studies were conducted. Different countries may exercise different regulations for use of sleep medications, some more strict than the others. For instance, the prevalence of use of sleep medications in Italy in 1996/1997 reported by Ohayon et al. was 5.7%,[188] but the prevalence in Portugal in 1998/1997 reported by Marques Vidal et al. was 13%.[189] Further, the studies by Ohayon et al.[188] and Marques-Vidal et al.[189] included all classes of drugs that may promote sleep, instead of specific to hypnotics and sedatives. These drugs (anxiolytics and antidepressants) may be prescribed differently in relation to obesity.

The effect of weight loss interventions on use of hypnotics and sedatives is not clear. One uncontrolled prospective cohort study showed increased use of hypnotics and sedatives (and decreased use of antidepressants in women) 2 years following gastric bypass surgery in 165 Norwegian patients.[192] Two other uncontrolled studies, have shown a decrease in overall "psychiatric" drug use (includes hypnotics, sedatives, anxiolytics and antidepressants) after bariatric surgery. [193] [194] One recently published Swedish study showed an increase in use of hypnotics and sedatives after gastric bypass surgery, compared to a general population control.[195] Note that in the Swedish study, difference in baseline BMI level between groups were not taken into account, and the general population group did not undergo any weight loss intervention. No randomised controlled trials have assessed the effect of weight loss interventions on use of hypnotics and sedatives, or sleep-promoting agents more broadly. It is not known whether weight loss interventions may help reduce use of sleep medications (originally prescribed for treating obesity-related sleep disorders, as found by Vozoris et al.[190]); or if a separate intervention is required. Prolonged use of sleep medication is not recommended given the adverse effects, but stopping use of sleep medications is often difficult due to concerns over withdrawal symptoms, and over physical or psychological dependence.

2.4. Literature gap

The main focus of this thesis is in the relationship between obesity and EDS, and the potential effect of weight loss interventions on daytime sleepiness. In this context, there were some gaps in the literature, prior to the commencement of this thesis:

- The extent to which the relationship between obesity and EDS is causal, is not clear
  Although prospective cohort studies have consistently found a significant association between obesity and weight gain with incident EDS,[151,175,176] or weight loss with EDS remission;[176] the extent to which these associations are causal is unclear. To infer causation from association in observational studies, the assumptions of no unmeasured confounding, positivity and well-defined interventions need to be fulfilled.[196] None of the existing studies have assessed the extent to which these assumptions are fulfilled in their studies.

  Randomised controlled studies on weight loss interventions provide an opportunity to assess causation between obesity and EDS. However, results thus far are have not been systematically synthesised (see below).

- The effect of weight loss interventions on EDS, and the role of the amount of weight loss in this effect, have not been formally synthesised
  Argahi et al and Ifthikhar et al have assessed EDS as an outcome of weight loss through lifestyle modification in their meta-analyses, but only as a secondary outcome to obstructive sleep apnea.[146,185] This results in the exclusion of studies that should otherwise be included, risking a biased conclusion. Further, neither of the two reviews performed a meta-regression analysis to assess the potential dose-reponse relationship between the amount of weight loss and the magnitude of change in daytime sleepiness.

- The potential pathways through which obesity may lead to EDS has not been formally assessed
  Following the indications that obesity-related EDS may occur independently of obstructive sleep apnea, there has been some hypotheses on the likely pathways through which obesity may lead to EDS;[186] but to our knowledge, no comprehensive pathway or mediation analyses (between obesity and EDS) has been performed.

The secondary focus of this thesis is in the potential effect of weight loss interventions on use of hypnotics and sedatives, and the potential consequences of having EDS in the general population. In this context, we have identified gaps in the literature:

- The effect of weight loss on use of hypnotics and sedatives is not known
  Studies assessing the effect of weight loss interventions on the use hypnotics and sedatives were limited by the absence of a control group,[192] lack of a suitable comparator group,[195] and lack of distinction between hypnotics and sedatives, with other sleep promoting agents such as anxiolytics and antidepressants,[193,194] which may behave differently with weight loss. The effect of weight loss on other sleep measures such as obstructive sleep apnea, insomnia or EDS, may not be directly translateable to the effect of weight loss on use of hypnotics and sedatives, due to issues with tolerance, dependence, and withdrawal symptoms.

- <u>There is limited evidence for the longitudinal relationship between EDS and incident disability</u>
  Park et al assessed the relationship between EDS and incident disability;[84] but in this analysis, EDS was combined with other masures of poor sleep (trouble falling asleep, waking up, and feeling unrested) as "dyssomnia". Also, the study was performed in the elderly (mean age 75 years) where the magnitude of association with disability is likely to be diminished. Moreover, minimum variables were included in the core adjustment set (demographic variables only). The remaining variables were included separately in different models. Another study by Nakakubo et al,[83] adjusted for a more complete set of potential confounders but the study was only performed in a Japanese population. The generalisability of their findings to other ethnic populations is unclear.

- <u>The relationship between EDS and mortality is not consistent and no studies thus far have assessed the impact of EDS-related mortality on life expectancy.</u>
  Of the four large population studies assessing the relationship between EDS and mortality, one study found no relationship between EDS and mortality but the remaining three found that EDS increases the risk of mortality, with inconsistent results on interaction by sex.[85,87,88] The discrepancies in results can perhaps be attributable to the use of different EDS definitions, EDS measurement tool, and the selection of confounder adjustment in the studies. Of all four studies, Empana et al.[85] may provide the strongest level of evidence, due to its adequate confounder adjustment, large sample size, and more appropriate measurement of EDS. However, the generalizability of their findings may be limited, due to their low response rate (37%). None of the studies thus far have assessed the impact of the relationship between EDS and mortality on life expectancy. Therefore, it is unclear whether EDS increases the risk of mortality in a more generally representative sample; and it is not known the extent to which the relationship between EDS and mortality may affect life expectancy.

2.5. Aims of this thesis

The primary aim of this thesis is to provide further understanding on the relationship between obesity and EDS and to determine the potential role of weight loss interventions in improving EDS (Part 1). In addition, this thesis also aims to assess the effect of weight loss interventions on use of sleep medications (Part 2), and to quantify the disability and mortality burden associated with having EDS (Part 3). Specific key objectives for each individual projects are summarised in the box below.

KEY OBJECTIVES

Part 1

- To quantify the prevalence of excessive daytime sleepiness in a general working population in Australia and identify its associated risk factors
- To assess the causal relationship between weight change and daytime sleepiness through a prospective cohort study
- To synthesise the effect of existing weight loss interventions on daytime sleepiness, and to study the role of the amount of weight loss in this effect
- To study the short- and long-term change in daytime sleepiness following a physical activity program in a general working population

Part 2

- To study the use of hypnotics and sedatives after gastric bypass surgery and intensive lifestyle modifications in Swedish adults with obesity

Part 3

- To assess the likelihood of developing disability and risk of mortality associated with having excessive daytime sleepiness, and its implications on life expectancy

2.6. Significance

Given the increasing global prevalence of obesity,[32] it is essential that we fully understand the consequences of obesity, to determine the extent to which obesity is a health priority and to help develop a more comprehensive management strategy for obesity. Of all areas of health that might be affected by obesity, sleep health is one of the most, if not the most, understudied area. This is despite the known catastrophic consequences of sleep problems on our overall health and well-being, quality of life, as well as work performance.[100] A more advanced understanding in obesity-related health problems can help improve the detection of sleep problems in obese individuals, and thus prevent its consequences from occurring.

Studying the relationship between obesity and EDS is crucial from the perspectives of sleep research because EDS is the most commonly encountered complaint in sleep clinics and its prevalence in the general population has been increasing.[98] A full identification and understanding of the potential contributors to EDS can help in the improvement of prevention, diagnosis, management strategy for EDS, which has been associated with a range of negative consequences such as increased risk of injury and accidents,[77,79] as well as reduced work and academic performances.[80,81]

Understanding the role of weight loss on sleep health is also important. If weight loss has the potential to improve sleep health, individuals with obesity may be more motivated to undertake a weight loss program (given the extra benefit), and weight loss programs can be further promoted as one of the non-pharmacological treatment options for sleep problems, which are often preferred considering the side effects, tolerance, dependence and withdrawal issues associated with most pharmacological treatments for sleep problems.

Despite the consequences of sleep problems,[100] most of which became immediately apparent and experienced in our daily lives, the importance of maintaining a good sleep health remains under-recognised in the general population. With increasing occupational constraints and social demands, sleep health is usually the first sacrificed. This general ignorance in the importance of sleep health is perhaps due to the lack of understanding in the extent to which sleep problems can be an issue. Quantifying the life expectancy loss associated with having sleep problems may provide further clarity and understanding to the importance of sleep health, for the general population more broadly.

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PART 1

Obesity and Excessive Daytime Sleepiness

CHAPTER 3

The cross-sectional relationship between obesity and excessive daytime sleepiness

"*In this study of a mixed population of employed Australian workers, the prevalence of excessive daytime sleepiness was estimated to be 16.0%. Several factors were found to be associated with excessive daytime sleepiness and increased Epworth Sleepiness Scale score, including age, higher body mass index, worse dietary habit, and poorer mental health status.*"

3.1. Summary

Prior to the commencement of this thesis, the prevalence of excessive daytime sleepiness estimated from previous studies widely varied, and the associations between excessive daytime sleepiness with potential risk factors such as age, sex, physical activity and body mass index were inconsistent. This can perhaps be attributed to the different tools used to measure daytime sleepiness, the unclear definition of excessive daytime sleepiness in earlier studies, and the focus on different types of higher risk population (such as shift-workers, bus drivers) instead of a more general working population. Thus, this study aimed to identify the prevalence of excessive daytime sleepiness, and to confirm the cross-sectional relationship between excessive daytime sleepiness with obesity and other potential risk factors, in a cohort of general Australian workers with mixed occupations. Through this study, we estimated that one in six Australian workers had excessive daytime sleepiness, as measured through Epworth Sleepiness Scale, the widely used tool to assess daytime sleepiness. We also confirmed that excessive daytime sleepiness is associated with obesity, and found that the two seem to share a range of risk factors such as poor dietary habits and poor mental health status.

3.2. Publication: The Prevalence and Characteristics Associated with Excessive Daytime Sleepiness Among Australian Workers

3.2.1. Declaration

In the case of Chapter 3, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Study design, literature synthesis, statistical analysis, integrity of the data and accuracy of the data analysis, critical interpretation of the data, drafting manuscript	80

Note that 50% of the work was done prior to the commencement of my PhD candidature

The following co-authors contributed to the work. If co-authors are students at Monash University, the extent of their contribution in percentage terms must be stated:

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
Anna Peeters	Study design, literature synthesis, statistical analysis, critical interpretation of the data, drafting manuscript	N/A
Rosanne Freak-Poli	Study design, literature synthesis, critical interpretation of the data, drafting manuscript	N/A

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the candidate's and co-authors' contributions to this work*.

Candidate's Signature			**Date** 17/03/2017
Main Supervisor's Signature			**Date** 17/03/2017

3.2.2. Manuscript

The prevalence and characteristics associated with excessive daytime sleepiness among Australian workers.

Liviya Ng W, Freak-Poli R, Peeters A.

J Occup Environ Med. 2014 Sep;56(9):935-45.

ORIGINAL ARTICLE

The Prevalence and Characteristics Associated With Excessive Daytime Sleepiness Among Australian Workers

Winda Liviya NG, BMedSc(Hons), Rosanne Freak-Poli, BSc, BHSc, PhD, and Anna Peeters, BSc(Hons), PhD

Objective: To estimate the prevalence of excessive daytime sleepiness (EDS) and its associated factors in a mixed population of employed Australian workers. **Methods:** Study participants ($n = 707$) were volunteers from various Melbourne workplaces, participating in a workplace physical activity program in 2008. Daytime sleepiness was assessed using the Epworth Sleepiness Scale (ESS), with EDS defined as ESS scores >10. **Results:** In this population of adult employees (40.0% male; mean age 40.2 ± 10.4 years), prevalence of EDS was 16.0%. Characteristics associated with EDS and higher ESS scores were age, higher body mass index, markers of poorer diet, and markers of poorer mental health. **Conclusions:** Excessive daytime sleepiness is potentially an important contributor to lower productivity and poorer mental health in the workplace. Our finding suggests that workplace health programs aimed at improving diet and body weight may also help alleviate EDS.

Excessive daytime sleepiness (EDS) refers to a symptom of increased sleep propensity, when one's intention is to remain awake.[1] Since the late 1960s, EDS has been viewed as a serious medical condition and research in this area has started to develop.[2] The recognition of its importance is likely to be related to the increasingly apparent consequences of EDS; such as increased risk of travel accidents[3–9] and work-related injuries,[3,10,11] decreased quality of professional[12–15] and academic performance,[16–18] and increased rate of work absenteeism.[19]

A number of epidemiological studies have been conducted to capture the prevalence of EDS and its associated factors.[16,20–22] Nevertheless, in studies conducted over the last decade, the estimated prevalence has varied widely (from 1.4% to 46%),[23–28] and potential risk factors such as age, sex, physical activity, and body mass index (BMI) have been inconsistently associated with EDS.[26,27,29–33] This inconsistency may be attributable to the difference in the characteristics of the study participants, as well as the nonunified concept and measurement tools for daytime sleepiness.[1,34] Thus far, a majority of the studies on EDS focused on general population samples, or specific at risk workers; and only a few assessed EDS in a population of workers with mixed occupations.[10,35–37] Understanding EDS within the workplace is important both because many consequences of EDS are work-related[10,12,13,24,38,39] and because the increasing prevalence of sedentary occupations,[40] obesity,[41] and diabetes[42] is likely to affect the prevalence of EDS.[29,43–47] Today, the concept of EDS has improved vastly, but there remains no gold standard to measure daytime sleepiness. The closest to a gold standard would be the objective measurement tools, such as the multiple sleep latency test. Nevertheless, because of technical, economical, and time restrictions, the Epworth Sleepiness Scale (ESS)—a validated, self-administered eight-item questionnaire—is often considered to be the best alternative to objective measurement tools for study populations.[1,26,48,49]

Using the ESS, this study aims to identify the prevalence of and characteristics associated with EDS in a cohort of Australian employees with mixed occupations. For this study we used the Global Corporate Challenge® Evaluation Study cohort, a cohort of 762 adults from a range of workplaces who volunteered to participate in a workplace physical activity program evaluation in 2008. A better understanding of the degree of EDS in a mixed population of employed workers, as well as the characteristics of people with EDS, is important to appropriately prioritize the identification and management of EDS in a workplace setting.

METHODS

Study Population

Melbourne workplaces, which participated in a 4-month workplace pedometer program called the Global Corporate Challenge® (GCC®), were approached to be study sites for the GCC® Evaluation Study—a prospective cohort study that assessed the effect of participation in the program in 2008 on various cardiovascular health risk factors. Participation in the GCC® Evaluation Study was voluntary, and consent was obtained from the workplace as well as the study participants. Eligible participants were (1) enrolled to the GCC® program in 2008, (2) aged 18 years or above, (3) qualified and willing to give informed consent, and (4) employed at a participating workplace. A more detailed description of the GCC® Evaluation Study can be found in previous publications.[50–52] This article uses the baseline characteristics of the study participants of the GCC® Evaluation Study to estimate the prevalence of EDS and identify the potential risk factors associated with EDS.

The GCC® Evaluation Study recruited 762 eligible study participants from participating workplaces in Melbourne, Australia, between April 16 and May 30, 2008. Pregnant women at baseline ($n = 4$) and study participants who did not complete the assessment for daytime sleepiness at baseline ($n = 51$) were excluded from the analysis, giving a sample size of 707.

Measurements

Data collection involved questionnaires, and anthropometric and biomedical measurements. Questionnaires were administered via a password-protected Web site, where the study participants gained access using their unique ID. The anthropometric and biomedical measurements were performed by trained staff.

Daytime sleepiness is the main outcome in this study and was measured via an internet-based questionnaire. It was assessed using the ESS, which is a validated, self-administered, eight-item

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This study was conducted in accordance with Monash University Human Research Ethics approval, specifically by the Standing Committee on Ethics in Research Involving Humans; Low Impact Research Project Involving Humans (Authorization number: CF08/0271- 2008000125).

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questionnaire.[53] The questions describe commonly encountered daily activities, and the responders are required to rate for each of the situations the chance of falling asleep (from 0 to 3). The total score ranges from 0 to 24, with higher scores reflecting a more severe level of daytime sleepiness.[1,53] EDS is defined as ESS scores >10, which was derived from mean ± 2 standard deviation of ESS scores from a previous study on Australian workers.[36]

Other baseline characteristics of the study participants from the GCC® Evaluation Study were treated as potential associated factors. The self-administered questionnaires included the following:

- Demographic information
- Dietary pattern assessed using the World Health Organization (WHO) STEPwise approach[54] and questions from Ball et al.[55]
- Behavioral measures assessed using the WHO STEPwise approach.[54]
- Psychosocial measures assessed using the WHO (five) index,[56,57] SF-12® Health Survey (version 1), and the Kessler 10 (K10) Symptom Scale.[58]

Anthropometric measurements included height, weight, waist circumference, and hip circumference using a 200-cm stadiometer, a 150-kg bathroom scale, and a Figure Finder tape measure to the nearest 0.1 cm, 0.1 kg, and 0.1 cm, respectively. Biomedical measurements included blood pressure and fasting blood profile on glucose, total cholesterol, and triglycerides. Before biomedical measurements, the study participants were required to fast for 10 to 12 hours, but no longer than 15 hours and refrain from smoking, exercise, or engaging in any activities that may result in pain, 1 hour before the allocated time of biomedical measurements. Table 1 provides the definitions for the categorical variables being used in this study.

Analysis

All statistical analyses were performed using STATA® version 10 (StataCorp, College Station, TX), with regression as the main mode of analysis to allow adjustment for clustering effects by workplaces. Linear regression was used to compare mean values of continuous outcomes and logistic regression to compare variables with categorical outcomes. For categorical variables with more than two outcomes (nonbinary), an ordered logistic regression model was used.

The prevalence of EDS in the overall study population (n = 707) was assessed as the proportion of study participants with ESS scores of more than 10. The baseline characteristics of the study participants who did and did not have EDS were compared to assess the potential risk factors associated with having EDS.

In the linear and logistic regression analyses, analysis was restricted to 538 participants, with complete data on all variables. The incomplete data were mostly on type of occupation, level of income, as well as anthropometric and biomedical measurements. Three multivariate approaches were applied to assess for associations with EDS, with variation in the adjustment to cofactors. The first model adjusted for age and sex, the second model for additional demographic characteristics, and the third model for all factors analyzed. In the multivariate model, if any two similar variables representing the same concept had significant correlation, only one of the variables was included in the model. Triglyceride level was log-transformed before entering the regression model as it was not normally distributed. Age was entered into the regression analyses as a quadratic variable.

RESULTS

The mean age of study participants was 40.2 ± 10.4 years, with 40.0% males and 79.8% who completed tertiary education (Table 2). The prevalence of EDS in this population was 16.0%. The study participants had relatively high socioeconomic profiles, habit of frequent snacking and eating takeaway food, long hours of sitting time, psychosocial measures bordering on poor levels, and high BMI scores. The prevalence of diabetes was 6.7% and hypertension was 28.1%.

Stratification by EDS status showed that study participants with EDS were more likely to be female, have lower income, lower sitting time during weekends, lower level of triglycerides, increased likelihood of having diabetes, and poorer psychosocial state as reflected by the lower well-being, lower SF-12 (mental functioning) and higher K10 scores (Table 2).

Although no association was observed between EDS and age (Table 2)—as a previous study[29] has observed a J-shaped relationship with age—we further analyzed the prevalence of EDS across age groups (Fig. 1), stratified by sex. In females, the distribution was almost U-shaped, and in males, prevalence increased from around age 50 years. Nevertheless, the numbers of study participants were relatively small in the youngest and oldest age/sex groups (<15% in each group). The proportion with EDS was greater in females than in males across all age groups.

Multivariate logistic regression analysis (Table 3) demonstrated that EDS was associated with age (as a quadratic term); meeting guidelines for fruit intake; higher frequency of takeaway food; eating while watching TV; less sitting time during weekends; poorer well-being; poorer mental functioning on the SF-12; greater psychological distress on the K10; as well as higher BMI, a higher heart rate; lower total cholesterol levels; and higher triglyceride levels.

Multivariate linear regression of participant characteristics on the ESS (Table 4) identified similar factors to those identified for EDS, except no relationship was found with fruit intake, heart rate, or cholesterol level. In addition, poorer physical functioning on the SF-12 was associated with higher (worse) ESS scores.

Note that no substantial differences with any of the results were found for models one and two when study participants with incomplete data were included in the analyses. Also, the prevalence of EDS remained the same (16%) after exclusion of study participants with incomplete data.

DISCUSSION

This study in a population of 707 Melbourne workers demonstrated a prevalence of EDS of 16.0%. Characteristics associated with a higher risk of EDS and the worse ESS were generally indicators of poorer health: older age; more frequent consumption of takeaway food; eating while watching TV; lower self-rated well-being; poorer mental functioning; greater psychological distress; as well as higher BMI; and higher triglyceride levels. In addition, EDS was associated with meeting guidelines for fruit intake, higher heart rate, and lower cholesterol, whereas the higher ESS was additionally associated with poorer physical functioning. The higher fruit intake, shorter duration of sitting time during weekends, and lower cholesterol observed associations were not expected, and were contrary to the other diet, physical functioning, and cardiovascular health associations observed for both EDS and ESS.

Our observed EDS prevalence of 16.0% is within the range identified by previous studies assessing working populations (3.5% to 46%).[11,24,25,28,35,38,69] As discussed in the introduction, the variety in previous studies can mainly be attributed to the fact that they generally involved specific cohorts of workers, combined with variability in measurement techniques. This study used the validated ESS to define and measure daytime sleepiness for a mixed population of workers, across a range of workplaces and occupations.

Our analyses suggest that older age (>50 years) is a significant predictor of EDS, whereas sex is not. To date, the relationships between EDS, age, and sex have been inconsistent.[26,27,29–31] Ohayon[27] proposed that this could be due to the lack of stratification of EDS by severity. Through Sleep-EVAL, a computerized interview software, they found that severe EDS was associated with young age and female sex, but moderate EDS was associated with older age, and

TABLE 1. Definitions for Categorical Variables

Variable	Description
Demographics	
SEIFA[59]	Residential postcodes were given SEIFA, a continuum of advantage to disadvantage derived from census data and then quartiled to Victorian norms
Completion of tertiary education[54]	The seven levels of education in the WHO STEPwise approach were dichotomized into nontertiary vs tertiary education
Occupation[60]	The nine major groups of occupations in the Australian Standard Classification of Occupations were further categorized to four groups (ie, "manager," "professional," "associate professional," and "clerical or service")
Dietary pattern	
Fruit intake[61–63]	
Meeting guidelines	≥2 servings per day
Vegetable intake[61–63]	
Meeting guidelines	≥4 servings per day
Takeaway food[55]	Categorized into "once or less per month," "about once a week," and "more than once a week."
Eating while watching TV	Categorized into "always," "often," "sometimes," "not very often," and "never"
Behavioral measures	
Alcohol intake[64]	
Meeting guidelines	≤2 standard drinks on any day
Non-tobacco smoker	Not a current smoker
Physical activity[61,62,65]	
Meeting guidelines	≥150 min of moderate-intensity activity/wk, preferably spread across at least five sessions over the week, with vigorous activity counted as double minutes
Anthropometric measures	
BMI[62]	
Normal	BMI 18.50 to ≤24.99 kg/m^2
Overweight	BMI 25.00 to ≤29.99 kg/m^2
Obese	BMI ≥30.00 kg/m^2
Waist circumference[66]	
Normal	Male: <94.0 cm; female: <80.0 cm
Increased	Male: 94.0–101.9 cm; female: 80.0–87.0 cm
Substantially increased	Male: ≥102.0 cm; female: ≥88.0 cm
Biomedical measures	
Hypertension status[62,67]	
No	Systolic blood pressure <140 and diastolic blood pressure <90 and without self-reported hypertension
Yes	Systolic blood pressure ≥140 and/or diastolic blood pressure ≥90 and/or with self-reported hypertension
Diabetes[68]	
No	Fasting blood glucose <7 mmol/L and without self-reported diabetes
Yes	Fasting blood glucose ≥7 mmol/L and/or with self-reported diabetes

BMI, body mass index; SEIFA, Socio-Economic Indexes for Areas.

had no association with sex. The ESS can also be used to estimate the severity of EDS,[70] but this study did not have enough power in the severe EDS category (ie, ESS >15; where $n = 15$, 2.8% of the sample) to assess the aforementioned hypothesis.

Previous studies have proposed that obesity is independently linked to EDS.[29,43,47,71] Of the two studies that used the ESS, one study found that higher BMI was associated with EDS and higher ESS scores, but it was conducted in a patient-based setting[71]; the other study found a significant association between higher BMI and EDS, but did not assess its association with the ESS as a continuous variable.[47] Using a mixed population of workers, this study found that high BMI was associated with both greater odds of EDS and higher ESS scores.

In this study, it was found that the higher frequency of takeaway food and eating while watching TV, two variables that have been linked with poor dietary content in previous studies,[72–76] were associated with increased likelihood of EDS and higher ESS scores. These results may support the theoretical relationship between EDS and poorer diet.[43] Nevertheless, there are some limitations to this finding, in particular the lack of detailed data on diet.

Previous studies have found a strong, significant association between mental health disorders with EDS.[23,26,27,29,31,44,69,77–79] Nevertheless, most of them focused on depression and only a few analyzed the association between EDS and general mental health. In this study, we found that poorer overall well-being and mental functioning, as well as psychological distress, were associated with an increased chance of EDS and higher ESS scores. Poorer physical functioning was associated with higher ESS scores, but not with EDS. Although, as in previous studies, the causal link cannot be determined because of the cross-sectional design of the study, these results further support the importance for clinicians to screen for mental health in patients with EDS.

In this study, diabetes was not associated with EDS or higher ESS scores. Theoretically, nocturia and neuropathic pain at night, as well as dysregulation of glucose levels in people with diabetes, could lower the quality of night-time sleep, causing EDS.[44,45,80,81] It

TABLE 2. Baseline Characteristics of the Study Participants

		ESS Categorization		
	Overall ($n = 707$)	Non-EDS* ($n = 594$)	EDS† ($n = 113$)	P‡
ESS, mean (SD)	6.6 (4.1)	5.3 (2.8)	13.4 (2.6)	<0.001
Demographics				
Age, mean (SD)	40.2 (10.4)	40.0 (10.1)	41.2 (12.0)	0.4
Sex, %				
Male	40.0	41.3	33.6	<0.001
Female	60.0	58.8	66.4	
Tertiary education, %	79.8	80.0	78.8	0.7
Occupation, %				
Manager	21.8	21.1	25.7	0.3
Professional	43.9	45.4	36.2	
Associate professional	18.5	18.0	21.0	
Clerical or service	15.8	15.5	17.1	
SEIFA, %				
Most advantaged	33.6	33.9	31.9	0.6
Advantaged	43.5	43.3	44.3	
Disadvantaged	16.4	16.5	15.9	
Most disadvantaged	6.5	6.2	8.0	
Income per week, %				
≥$2000	47.5	49.8	35.0	0.003
$1600–$1999	17.6	17.1	20.4	
$1000–$1599	23.8	22.4	31.1	
$0–$999	11.1	10.6	13.6	
Dietary pattern				
Fruit intake (meeting guidelines), %	30.3	29.8	32.7	0.5
Vegetable intake (meeting guidelines), %	14.6	15.0	12.4	0.3
Takeaway food, %				
Once or less per month	45.0	46.3	38.1	0.1
About once a week	41.4	41.3	42.5	
More than once a week	13.6	12.5	19.5	
Eating while watching TV, %				
Always	12.2	10.8	19.5	0.2
Often	39.6	40.9	32.7	
Sometimes	24.1	23.6	26.6	
Not very often	19.1	19.4	17.7	
Never	5.1	5.4	3.5	
Behavioral measures				
Alcohol (meeting guidelines), %	43.0	43.1	42.8	0.9
Non-tobacco smoker, %	89.8	90.2	87.6	0.4
Physical activity (meeting guidelines), %	38.2	39.4	31.9	0.1
Sitting time, hrs/d				
Weekday, mean (SD)	8.1 (3.6)	8.1 (3.5)	8.3 (4.1)	0.5
Weekend, mean (SD)	5.3 (3.0)	5.3 (3.0)	4.8 (2.8)	0.05
Psychosocial measures				
Well-being, mean (SD)	15.0 (4.8)	15.3 (4.5)	13.2 (5.8)	<0.001
SF-12, mean (SD)				
Physical functioning	50.5 (7.3)	50.7 (7.1)	49.5 (7.9)	0.06
Mental functioning	49.4 (10.0)	50.3 (9.4)	45.1 (11.8)	<0.001
K10, mean (SD)	17.8 (5.8)	17.2 (5.4)	21.2 (6.7)	<0.001
Anthropometric measures				
Body mass index, %				
Normal	41.1	42.3	35.0	0.2
Overweight	38.1	37.3	42.0	
Obese	20.8	20.4	23.0	

(*Continued*)

TABLE 2. (*Continued*)

		ESS Categorization		
	Overall ($n = 707$)	**Non-EDS* ($n = 594$)**	**EDS† ($n = 113$)**	***P*‡**
Waist circumference, %				
Normal	46.0	47.5	38.0	0.1
Increased	24.5	24.5	25.0	
Substantially increased	29.5	28.1	37.0	
Biomedical measures (fasting)				
Heart rate—beats/min—mean (SD)	68.6 (10.0)	68.5 (9.7)	69.4 (11.6)	0.3
Hypertension, %	28.1	27.4	31.73	0.3
Total cholesterol, mmol/L, mean (SD)	4.9 (0.9)	4.9 (0.9)	4.8 (0.9)	0.2
Diabetes, %	6.7	5.6	12.5	0.02
Triglycerides, mmol/L, mean (SD)	1.1 (0.8)	1.1 (0.8)	1.0 (0.6)	0.05

*Study participants without excessive daytime sleepiness, defined as ESS 10 or less.
†Study participants with excessive daytime sleepiness, defined as ESS more than 10.
‡For comparison between non-EDS and EDS groups.
EDS, excessive daytime sleepiness; ESS, Epworth Sleepiness Scale; SD, standard deviation; SEIFA, Socio-Economic Indexes for Areas.

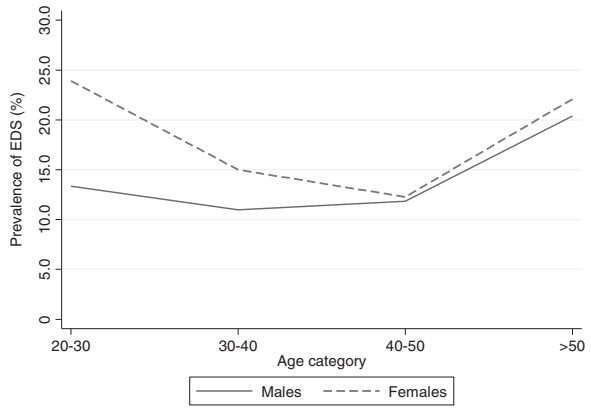

FIGURE 1. Distribution of excessive daytime sleepiness stratified by sex and age group.

is likely that an association was not found in this study because there were not enough participants with diabetes ($n = 39$; 7.3% of sample). Another finding from this study is the relationship between cardiovascular markers and EDS. Contrary to previous studies,[26,47,82] this study found a significant link between higher triglyceride levels, higher heart rate, and EDS. Nevertheless, Drager et al[83] found that the association between EDS and cardiovascular markers could be dependent on obstructive sleep apnea, one of the most common causes of EDS.[48,70] Future studies are needed to clarify the relationship between cardiovascular markers and EDS, independent from other sleep disorders.[19,21,22,24–26,75,77–80,82]

Some findings in this study contradicted our expectations. First, lower total cholesterol (a marker of good cardiovascular health) was found to be associated with EDS. Nevertheless, Empana et al,[82] reporting a similar finding, suggests that this might be driven by low high-density lipoprotein cholesterol (a marker of poor cardiovascular health). We were unable to assess this within this study. Second, adequate fruit intake, which reflects good nutritional status, was associated with EDS and worse ESS. This disagrees with our findings on the associations between markers of poorer diet with EDS and worse ESS. Third, lesser weekend sitting time, which was thought to be preventive of EDS, was shown to be associated with EDS and higher ESS. Nevertheless, less physical functioning was associated with the ESS. Because these data were collected through self-reported questionnaires, the possibility of under-/overreporting and recall errors can be considered, along with the possibility that they are statistical artifacts that result from multiple significance tests.

Strengths

The greatest strength of this study was the inclusion of a mixed population of employees as the study population. Previous studies on the prevalence and risk factors of occupational EDS have mostly targeted specific at-risk workers, with results consequently not applicable to a more diverse population of workers. To the best of our knowledge, in the past decade there was only one study on a rather mixed cohort of office workers, and that was in Japan.[35]

A further strength was the use of the ESS to measure daytime sleepiness. As discussed in the introduction, we have chosen the best alternative to an objective measurement tool, the ESS, which has been validated against these objective measurement tools,[49,53,81,84] and is now widely used in population studies.[1,26,48]

An additional strength was the extensive variables available in this study, which enabled us to explore a number of risk factors of EDS. As a result, we have identified a new potential correlation between poor dietary behavior and EDS. We have also demonstrated an important association between EDS and the continuum of mental well-being.

Limitations

The primary limitation of this study is the use of the self-reported ESS questionnaire to measure daytime sleepiness. Even though the ESS has been previously validated,[53,84] there are still some limitations that need to be considered. First, it is possible that not all fully understand the definition of EDS (ie, "the increased propensity to fall asleep when one intends to stay awake"), which may lead to some measurement inaccuracy. Second, the ESS is a self-reported questionnaire; hence with it, comes the limitations from the responder's mood, perception, and education level.[1,34] Nevertheless, considering the technical, financial, and time constraints from using objective measurement tools,[1,26,34] and the less accurate results from other questionnaires,[1,53] the ESS is regarded as the best available option for epidemiological studies such as this.

Another potential limitation is the general selection bias that results from the voluntary recruitment of the study participants.[51] The study participants have higher educational status than the

TABLE 3. Participant Characteristics Associated With Excessive Daytime Sleepiness

		Multivariate 1*		Multivariate 2†		Multivariate 3‡	
Predictor Variable	***n* (% With EDS)**	**Odds Ratio**	***P***	**Odds Ratio**	***P***	**Odds Ratio**	***P***
Demographics							
Age							
Years	538	0.80	0.001	0.81	0.004		
Years^2	538	1.00	0.001	1.00	0.001		
Sex							
Male	218 (15.1)	Reference					
Female	320 (15.9)	1.02	0.9	0.99	1.0		
Tertiary education							
Not completed	93 (18.3)	Reference					
Completed	445 (15.1)	0.81	0.4	0.94	0.8		
Occupation							
Manager	109 (17.4)	Reference					
Professional	246 (13.4)	0.67	0.2	0.65	0.1		
Associate professional	102 (16.7)	0.92	0.9	0.80	0.7		
Clerical or service	81 (18.5)	0.96	0.9	0.79	0.6		
SEIFA							
Most advantaged	185 (13.0)	Reference					
Advantaged	229 (17.5)	1.41	0.1	1.29	0.2		
Disadvantaged	89 (15.7)	1.22	0.5	1.07	0.8		
Most disadvantaged	35 (17.1)	1.42	0.6	1.18	0.8		
Income per week							
≥$2000	254 (11.8)	Reference					
$1600–$1999	98 (19.4)	1.71	0.06	1.70	0.07		
$1000–$1599	133 (18.1)	1.58	0.09	1.61	0.07		
$0–$999	53 (20.8)	1.46	0.3	1.40	0.4		
Dietary pattern							
Fruit intake							
Meeting guidelines	172 (18.0)	Reference					
Not meeting guidelines	366 (14.5)	0.81	0.4	0.8	0.3	0.52	0.003
Vegetable intake							
Meeting guidelines	81 (14.8)	Reference					
Not meeting guidelines	457 (15.8)	1.13	0.6	1.1	0.8	1.09	0.8
Takeaway food							
Once or less per month	247 (13.4)	Reference					
About once a week	220 (15.0)	1.25	0.4	1.25	0.4	1.47	0.2
More than once a week	71 (25.4)	2.37	0.001	2.62	0.001	4.55	<0.001
Eating while watching TV							
Always	70 (27.1)	Reference					
Often	216 (12.0)	0.35	<0.001	0.35	<0.001	0.23	<0.001
Sometimes	120 (17.5)	0.54	0.05	0.55	0.03	0.47	0.07
Not very often	102 (14.7)	0.44	0.02	0.45	0.01	0.34	0.02
Never	30 (10.0)	0.30	0.02	0.32	0.02	0.45	0.1
Behavioral measures							
Alcohol							
Not meeting guidelines	313 (16.0)	Reference					
Meeting guidelines	225 (15.1)	0.91	0.7	0.9	0.8	1.01	1.0
Non-tobacco smoker							
Nonsmoker	484 (15.5)	Reference					
Smoker	54 (16.7)	1.04	0.9	1.0	1.0	1.14	0.8
Physical activity							
Meeting guidelines	217 (12.4)	Reference					
Not meeting guidelines	321 (17.8)	1.63	0.05	1.6	0.04	1.45	0.2

(*Continued*)

TABLE 3. (*Continued*)

		Multivariate 1*		Multivariate 2†		Multivariate 3‡	
Predictor Variable	***n* (% With EDS)**	**Odds Ratio**	***P***	**Odds Ratio**	***P***	**Odds Ratio**	***P***
Sitting time, per hour per day							
Weekday	538	1.02	0.7	1.0	0.6	1.03	0.4
Weekend	538	0.94	0.04	0.9	0.06	0.85	<0.001
Psychosocial measures							
Well-being§	538	0.89	<0.001	0.90	<0.001	0.88	<0.001
SF-12§							
Physical functioning	538	0.98	0.1	0.98	0.2	0.96	0.08
Mental functioning	538	0.95	<0.001	0.95	<0.001	0.93	<0.001
K10§	538	1.12	<0.001	1.11	<0.001	1.13	<0.001
Anthropometric measures							
Body mass index‖							
Normal	226 (12.4)	Reference					
Overweight	206 (17.5)	1.64	0.02	1.54	0.08	1.78	0.04
Obese	106 (18.9)	1.75	0.1	1.58	0.2	1.36	0.4
Waist circumference‖							
Normal	255 (12.9)	Reference					
Increased	130 (16.2)	1.30	0.3	1.26	0.4	0.94	0.8
Substantially increased	153 (19.6)	1.72	0.1	1.58	0.2	1.37	0.5
Biomedical measures							
Heart rate, beats/min	538	1.02	0.01	1.02	0.03	1.03	0.001
Hypertension							
Normal	383 (14.6)	Reference					
Hypertensive	155 (18.1)	1.28	0.3	1.24	0.4	1.15	0.5
Total cholesterol, mmol/L	538	0.77	0.002	0.77	0.01	0.81	0.04
Diabetes status							
Nondiabetic	499 (14.6)	Reference					
Diabetic	39 (28.2)	2.28	0.08	2.19	0.1	2.70	0.07
Triglycerides, mmol/L	538	2.00	0.02	1.89	0.01	1.53	0.003

*Adjusted for age and sex.
†Adjusted for all demographic variables.
‡Adjusted for all factors within the table, except for SF-12 and K10. The demographic variables were not adjusted for all other factors.
§Because of the strong correlation between well-being, SF-12, and K10 scores, each was analyzed in a different multivariate model, in such a way that they were not mutually adjusted.
‖Because of the strong correlation between body mass index and waist circumference, each was analyzed in a different multivariate model, in such a way that they were not mutually adjusted.
EDS, excessive daytime sleepiness; SEIFA, Socio-Economic Indexes for Areas.

general population and may also have a better health profile than the general working population because they are a motivated cohort of people who are concerned enough about their health to participate in a workplace health program. The effect of any such bias is likely to be an underestimation of the prevalence of EDS and potentially of the strength of the associations presented here. Even so, the validity of the internal relationship is unlikely to be biased. Moreover, in a previous comparison of this volunteer group with the general Australian adults,[51] similar differences in the risk profile were observed.

An additional limitation was the assessment of daytime sleepiness as a secondary outcome of interest in the GCC® Evaluation study. This limited some of our analyses. We suggest that future research ensure a sufficient number of participants in the extreme age groups, as well as participants with obesity and diabetes, to better assess the relationships between these factors and EDS. Furthermore, a more detailed dietary measurement should be included to allow comprehensive analysis on the hypothetical relationship between diet and EDS.

IMPLICATIONS

The results reported here suggest that approximately one in six Australian workers have EDS, a condition which has been consistently associated with increased mortality[3,9] and productivity loss.[14,19] Nevertheless, to our knowledge, the monitoring for EDS in workplaces is relatively uncommon. Future workplace health promotion programs should include EDS as one of the key health areas to be monitored, especially those programs targeting noncommunicable diseases (NCDs) and obesity, as they seem to share a similar range of risk factors.

The shared risk factors between EDS, obesity, and NCDs also suggest that the increasingly common health programs targeting obesity and NCDs may have further benefits through improvement in EDS. This warrants further study. If so, this additional unforeseen benefit of workplace health promotion program may trigger more support from the participating employers. In addition, our findings on the correlates of EDS provide a collective array of potential health factors that can be targeted in future workplace intervention programs to alleviate EDS.

TABLE 4. Participant Characteristics Associated With Epworth Sleepiness Scale

			Multivariate 1*		Multivariate 2†		Multivariate 3‡	
Predictor Variable	***n***	**Mean ESS**	**Coefficient**	***P***	**Coefficient**	***P***	**Coefficient**	***P***
Demographics								
Age (quadratic)								
Years	538	–	−0.46	0.01	−0.45	0.01		
Years^2	538	–	0.01	0.002	0.01	0.01		
Sex								
Male	218	6.3 ± 4.0	Reference					
Female	320	6.8 ± 4.0	0.42	0.2	0.40	0.3		
Tertiary education								
Not completed	93	6.7 ± 4.0	Reference					
Completed	445	6.5 ± 4.0	−0.09	0.8	0.06	0.9		
Occupation								
Manager	109	6.9 ± 4.1	Reference					
Professional	246	6.2 ± 4.1	−0.80	0.1	−0.84	0.06		
Associate professional	102	6.8 ± 4.0	−0.17	0.8	−0.24	0.6		
Clerical or service	81	6.8 ± 3.8	−0.43	0.6	−0.56	0.5		
SEIFA								
Most advantaged	185	6.3 ± 3.7	Reference					
Advantaged	229	6.9 ± 4.3	0.56	0.2	0.43	0.3		
Disadvantaged	89	6.4 ± 3.8	−0.02	1.0	−0.18	0.6		
Most disadvantaged	35	5.9 ± 4.0	−0.47	0.5	−0.69	0.4		
Income per week								
≥$2000	254	6.2 ± 3.9	Reference					
$1600–$1999	98	6.9 ± 4.1	0.51	0.4	0.54	0.3		
$1000–$1599	133	6.6 ± 3.9	0.24	0.5	0.36	0.3		
$0–$999	53	7.4 ± 4.9	0.41	0.5	0.46	0.5		
Dietary pattern								
Fruit intake								
Meeting guidelines	172	6.7 ± 4.3	Reference					
Not meeting guidelines	366	6.5 ± 3.9	−0.04	0.9	0.00	1.0	−0.48	0.2
Vegetable intake								
Meeting guidelines	81	6.2 ± 3.7	Reference					
Not meeting guidelines	457	6.6 ± 4.1	0.50	0.2	0.46	0.2	0.22	0.6
Takeaway food								
Once or less per month	247	6.1 ± 4.0	Reference					
About once a week	220	6.9 ± 4.0	1.01	0.04	0.99	0.05	1.01	0.04
More than once a week	71	7.3 ± 3.9	1.43	0.004	1.55	0.004	1.59	0.003
Eating while watching TV								
Always	70	7.9 ± 4.8	Reference					
Often	216	6.6 ± 3.7	−1.32	0.02	−1.29	0.02	−1.52	0.01
Sometimes	120	6.5 ± 4.1	−1.35	0.08	−1.37	0.07	−1.35	0.08
Not very often	102	6.0 ± 3.9	−1.84	0.03	−1.89	0.02	−1.85	0.02
Never	30	5.0 ± 3.5	−2.74	0.02	−2.64	0.04	−1.96	0.07
Behavioral measures								
Alcohol								
Not meeting guidelines	313	6.7 ± 4.1	Reference					
Meeting guidelines	225	6.3 ± 3.9	−0.47	0.3	−0.37	0.3	−0.26	0.5
Non-tobacco smoker								
Nonsmoker	484	6.5 ± 4.0	Reference					
Smoker	54	6.9 ± 4.0	0.18	0.8	0.15	0.8	−0.05	0.9
Physical activity								
Meeting guidelines	217	6.3 ± 4.0	Reference					
Not meeting guidelines	321	6.8 ± 4.0	0.59	0.04	0.63	0.03	0.34	0.2

(*Continued*)

TABLE 4. (*Continued*)

			Multivariate 1*		Multivariate 2†		Multivariate 3‡	
Predictor Variable	***n***	**Mean ESS**	**Coefficient**	***P***	**Coefficient**	***P***	**Coefficient**	***P***
Sitting time per hour per day								
Weekday	538	–	0.08	0.3	0.07	0.3	0.07	0.3
Weekend	538	–	−0.01	0.7	−0.01	0.8	−0.14	0.004
Psychosocial measures								
Well-being§	538	–	−0.18	0.001	−0.17	0.001	−0.15	0.01
SF-12§								
Physical functioning	538	–	−0.06	0.003	−0.06	0.002	−0.07	0.01
Mental functioning	538	–	−0.08	0.01	−0.08	0.01	−0.09	0.004
K10§	538	–	0.22	<0.001	0.22	<0.001	0.19	<0.001
Anthropometric measures								
Body mass index‖								
Normal	226	6.0 ± 4.1	Reference					
Overweight	206	6.7 ± 3.9	0.96	0.01	0.87	0.03	0.84	0.04
Obese	106	7.4 ± 3.8	1.57	0.01	1.50	0.01	1.13	0.03
Waist circumference‖								
Normal	255	6.1 ± 4.0	Reference					
Increased	130	6.9 ± 4.1	0.74	0.1	0.72	0.1	0.44	0.3
Substantially increased	153	7.0 ± 3.9	0.93	0.04	0.89	0.06	0.43	0.3
Biomedical measures								
Heart rate, beats/min	538	–	0.02	0.3	0.01	0.4	0.01	0.2
Hypertension								
Normal	383	6.4 ± 3.9	Reference					
Hypertensive	155	6.9 ± 4.2	0.57	0.2	0.57	0.2	0.25	0.5
Total cholesterol, mmol/L	538	–	−0.23	0.1	−0.23	0.1	−0.22	0.2
Diabetes status								
Nondiabetic	499	6.4 ± 4.0	Reference					
Diabetic	39	8.0 ± 4.1	1.49	0.1	1.57	0.1	1.34	0.1
Triglycerides, mmol/L	538	–	0.82	0.2	0.76	0.2	0.45	0.01

*Adjusted for age and sex.
†Adjusted for all demographic variables.
‡Adjusted for all factors within the table, except for SF-12 and K10. The demographic variables were not adjusted for all other factors.
§Because of the strong correlation between well-being, SF-12, and K10 scores, each was analyzed in a different multivariate model, in such a way that they were not mutually adjusted.
‖Because of the strong correlation between body mass index and waist circumference, each was analyzed in a different multivariate model, in such a way that they were not mutually adjusted.
ESS, Epworth Sleepiness Scale; SEIFA, Socio-Economic Indexes for Areas.

CONCLUSIONS

In this study of a mixed population of employed Australian workers, the prevalence of EDS was estimated to be 16.0%. Several factors were found to be associated with EDS and increased ESS, including age, higher BMI, worse dietary habit, and poorer mental health status. These findings may contribute to the better identification and targeting of workers with EDS in potential future interventions to alleviate EDS; and in clinical settings, to improve screening for EDS in patients with the aforementioned risk factors. It will be important to determine whether interventions on the identified risk factors are able to improve EDS.

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CHAPTER 4

The relationship between weight change and daytime sleepiness

"Weight gain has a detrimental effect on daytime sleepiness, mostly through pathways other than OSA. This study provides further evidence and understanding to the relationship between obesity and excessive daytime sleepiness."

4.1. Summary

In this chapter, we set out to assess the relationship between weight change and daytime sleepiness, using the Sleep Heart Health Study dataset; a longitudinal study on sleep and cardiovascular health in 6,441 community-dwelling American adults. A causal framework was applied, where we selected potential confounders for adjustment in the analysis through a causal diagram, and explicity identified and outlined the conditions under which our identified association may have a causal interpretation. We also explored the extent to which obstructive sleep apnea may mediate the relationship between weight change and daytime sleepiness, and similarly the role of other potential mediators, including mental health, physical health, and sleep duration. Our result suggests that weight gain is associated with worse daytime sleepiness; and there is a significant interaction by sex, where the relationship was only evident in women. Approximately one-fifth of the relationship between weight gain and daytime sleepiness is mediated by the severity of obstructive sleep apnea, and approximately one-sixth through poor physical health. We did not find evidence for mediation through sleep duration and mental health. Our findings further support the hypothesised causal relationship between obesity and excessive daytime sleepiness, and adds to the understanding of the potential pathways through which obesity may affect excessive daytime sleepiness. With a similar framework, future study needs to confirm our finding using a more robust dataset with lower rate of loss to follow-up and assess the temporal direction of the relationship between obesity and excessive daytime sleepiness. We also recommend future studies to explore the potential mediating role of more specific indicators of poor physical or mental health, such as asthma, depression, glucose level, and inflammatory markers, in the relationship between obesity and excessive daytime sleepiness.

4.2. Publication: The relationship between weight change and daytime sleepiness: The Sleep Heart Health Study

4.2.1. Declaration

In the case of Chapter 4, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Study design, literature synthesis, statistical analysis, integrity of the data and accuracy of the data analysis, critical interpretation of the data, drafting manuscript	80%

The following co-authors contributed to the work. If co-authors are students at Monash University, the extent of their contribution in percentage terms must be stated:

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
Liliana Orellana	Study design, statistical analysis, integrity of the data and accuracy of the data analysis, critical interpretation of data, drafting manuscript	N/A
Jonathan Shaw	Study design, critical interpretation of data, drafting manuscript	N/A
Evelyn Wong	Study design, critical interpretation of data, drafting manuscript	N/A
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The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the candidate's and co-authors' contributions to this work*.

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4.2.2. Manuscript

The relationship between weight change and daytime sleepiness: The Sleep Heart Health Study

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ABSTRACT

Objective Through a causal framework, we aim to assess the association between weight change and daytime sleepiness, and the role of obstructive sleep apnea (OSA) in this relationship.

Methods From the Sleep Heart Health Study, we selected individuals who were: 1) 40 to 64 years old, with 2) body mass index (BMI) ≥18.5 kg/m^2, 3) no history of stroke, treatment for OSA, and tracheostomy at baseline. We used multiple linear regression to assess the relationship between 5-year weight change and daytime sleepiness (assessed through Epworth Sleepiness Scale (ESS)) at 5 years, adjusting for daytime sleepiness, demographics, diabetes, subjective sleep duration, sleep disturbance, smoking status, weight, and use of antidepressants and benzodiazepines at baseline, in those with complete data (n=1,468). We further assessed the potential mediating role of OSA in this relationship.

Results At baseline, the study participants were on average 55 years old, 46% males, with mean BMI 28 kg/m^2; and 25% had ESS>10. ESS at 5 years worsened by 0.36 units (95%CI 0.12 – 0.61, P=0.004) with every 10 kg weight gain. When stratified by sex, this relationship was only found in women (0.55, 95%CI 0.25-0.86, p<0.001; p-interaction=0.02). Approximately one-fifth of the relationship between weight change and daytime sleepiness was mediated by severity of OSA at 5 years.

Conclusions Weight gain has a detrimental effect on daytime sleepiness, mostly through pathways other than OSA. This study provides further evidence and understanding to the relationship between obesity and excessive daytime sleepiness.

Keywords: obesity; weight change; daytime sleepiness; causal inference; causal mediation; obstructive sleep apnea

Introduction

The association between obesity and excessive daytime sleepiness (EDS) has long been accepted; but to our knowledge, its causality has not been formally assessed. Whether weight change has a causal effect on daytime sleepiness, and what the pathways are remain largely unexplored. EDS, the irresistible urge to fall asleep despite one's intention to remain awake,[1] is highly prevalent in the general population (up to 30%)[2] and is known to affect work performance,[3,4] mental health,[5] quality of life[5] and motor vehicle-related deaths.[6,7]

A recent longitudinal study by Fernandez et al[8] found that weight gain over 7.5 years was associated with incident and persistent EDS over the same duration; whilst weight loss was associated with its remission. Similarly, in another study by Palm et al.,[9] increase in body mass index (BMI) over 10-13 years was associated with incident EDS over the same duration. However, these studies used one/two-item non-validated questionnaire to assess EDS, and they did not assess potential mediating pathways between weight change and daytime sleepiness, which may provide useful information for interventions targeting EDS remission. Further, these observational studies did not explicitly describe the assumptions that need to be made to infer causation from their identified associations (between weight or BMI change, with EDS), i.e. the assumptions of no unmeasured confounding, well-defined interventions (consistency) and positivity (i.e. a non-zero chance of being treated).[10]

Using the Sleep Heart Health Study (SHHS) dataset, a large population-based multicentre cohort study for assessing the cardiovascular outcomes of sleep apnea, and a causal framework, we aimed to study the relationship between weight change and daytime sleepiness, measured through the Epworth Sleepiness Scale, a validated,[11] and widely-used eight-item questionnaire to measure daytime sleepiness. We also performed mediation analyses to assess the likely pathways through which weight change may affect daytime sleepiness. Potential mediators considered include obstructive sleep apnea, mental health, physical health, and sleep duration, as suggested by a previous review.[12]

Methods

Data source

We used the SHHS dataset; a large population-based multi-centre cohort study in the US, which aimed to assess the cardiovascular outcomes of sleep apnea in community-dwelling adults. 6,441 individuals were recruited from six on-going, population-based, parent cohorts: Atherosclerosis Risk in Communities Study, Cardiovascular Health Study, Framingham Heart Study, New York Cohorts, Strong Heart Study and Tucson Cohorts. To be recruited into the SHHS, individuals were required to be 40 years or older, with no history of treatment for sleep apnea or tracheostomy, and were not undertaking home oxygen therapy. There was oversampling of habitual snorers for younger participants (≤65 years old) to increase the prevalence of sleep apnea. The recruitment took place during routine study visits of the parent cohorts or through mail and telephone.

The SHHS baseline data was collected between December 1995 and February 1998. The first follow-up visit took place approximately 2-3 years after baseline (hereafter, referred to as 2-year follow-up); and the second follow up-visit, in another 2-3 years time, between 2001 and 2003 (hereafter, referred to as 5-year follow-up). Further information regarding the SHHS can be found in previous publications or the SHHS website.[13,14] Full information on the method of data collection and availability of the exposure, covariate and outcome variables throughout the study time-points are summarised in Table A.1 in the Supplement.

We obtained the SHHS dataset online, through the National Sleep Research Resource.[14,15] This version of the SHHS dataset excludes participants from the Strong Heart Study (n=637) due to issues with sovereignty.

Inclusion criteria for the current study

From the 5,804 study participants at baseline, we excluded those aged 65 years or older and those with history of stroke, as they are more likely to experience unhealthy weight loss. We also excluded those with history of treatment for sleep apnea or of tracheostomy, to be consistent with the SHHS study protocol (a small number of study participants undertook treatment for sleep apnea between recruitment and baseline data collection). We also excluded those with BMI <18.5 kg/m^2 due to the small number of such participants (n=10) and the concern that they may behave differently to the rest of the study sample.

A total of 3,028 study participants fulfilled our inclusion criteria (**Figure 1**), out of whom 1,468 study participants had complete exposure, confounders and outcome data at baseline and 5-year follow-up; 1,106 study participants at baseline and 2-year follow-up; and 649 study participants at baseline, 2-year and 5-year follow-up.

Primary study sample

The primary analyses was performed on the subset of 1,468 participants with complete data at baseline and 5-years to minimize missing data and attending to the fact that the potential mediators were only measured at these time points.

Exposure

The main exposure of this study was weight change (kg) between baseline and 5-year follow-up. At both time-points, weight was measured in light clothes, on a portable scale.

Outcome

The outcome of this study was daytime sleepiness assessed through the Epworth Sleepiness Scale (ESS). The ESS is a self-reported questionnaire, consisting of 8 commonly-encountered daily activities, for each the responders are asked to rate from 0 to 3, with the increasing likelihood of falling asleep.[16] EDS is defined as ESS>10. ESS has been previously shown to have good test-retest reliability for an individual over time,[17] and has moderate association with objective daytime sleepiness measured through multiple sleep latency test.[11,16]

Mediators

The potential mediators considered in this study included the obstructive apnea-hypopnea index (OAHI), respiratory disturbance index (RDI), mental and physical health, as well as objective and subjective sleep duration; all measured at 5-year follow-up (as well as baseline).

OAHI is defined as the number of obstructive apnea and hypopnea events with 4% oxyhemoglobin desaturation level or more, divided by total sleep time. RDI was defined as the number of apnea and hypopnea events with 4% oxyhemoglobin desaturation level or more, divided by total sleep time. Apnea was identified as (near) complete cessation of airflow (<25% of baseline, measured through amplitude of thermocouple signal) for at least 10 seconds. Hypopnea was identified as partial cessation of airflow (25%-70% of baseline) for at least 10 seconds. Apnea and hypopnea events were both assessed through an overnight polysomnography using a portable system (PS-2 System; Compumedics Limited, Abbotsford, Victoria, Australia).[18] Mental health was assessed through mental component score, and physical health through physical component score, of Short-Form 36.[19] Both mental and physical components are summary scores from eight domains of the Short-Form 36: physical functioning, role limitations due to physical problems, role limitations due to emotional problems, mental health, energy, vitality, pain, and general perception of health. Objective sleep duration was assessed through total sleep time from polysomnography, and subjective sleep duration, from a self-reported questionnaire ("*How many hours do you usually get at night (or your main sleep period) on weekdays or workdays/weekends*?" – Average sleep duration was calculated as (5*hours spent sleeping on workdays + 2*hours spent sleeping on weekdays)/7).[14]

We assumed that mediators measured at the same time as the outcome can still be considered intermediate variables between the exposure and the outcome.

Potential confounders

The confounders to be adjusted in the analyses were identified through a directed acyclic graph (DAG, Fig. A.1 in the Supplement),[20] built using DAGitty v.2.3. All relevant variables in the DAG were identified through our prior knowledge and previous research publications in the subject areas, irrespectively of their availability in the dataset.[21]

According to our DAG, the minimal sufficient adjustment set for producing an unbiased estimate of the total effect of weight change on daytime sleepiness includes the following baseline covariates: age, sex, race, socioeconomic position, circadian rhythm sleep-wake disorder, diabetes status, poor night sleep, smoking status, weight, use of antidepressants, anxiolytics and hypnotics/sedatives, weight and level of daytime sleepiness. We used education as a proxy for socioeconomic position, subjective sleep duration and sleep disturbance as a proxy for poor night sleep, and use of benzodiazepines as a proxy for use of anxiolytics and hypnotics/sedatives. The presence of circadian rhythm sleep-wake disorders was not measured in the SHHS.

We did not identify any other exposure-mediator, or mediator-outcome confounders that were not already considered as exposure-outcome confounders.

Statistical analysis

All analyses were performed using STATA® version 14.

Baseline characteristics, and levels of exposure and outcome

We summarized the baseline covariates, and the levels of exposure and outcome, for our total analysis population, as well as stratified by sex. The between-sex differences were compared using least squares linear regression for continuous variables, and logistic regression for categorical variables.

Attrition analysis

We compared the baseline covariates, exposure, and outcome values of 1,468 study participants included in the analysis with other eligible study participants excluded due to incomplete data on exposure, any of the covariates in the minimum set of confounders, or outcome using independent t-test for continuous variables and chi-square test for categorical variables.

Association between baseline covariates and exposure (5-year weight change)

The association between 5-year weight change and baseline covariates was estimated using (multiple) linear regression, 1) without any adjustment, 2) adjusting for age and sex.

Association between baseline covariates and outcome (ESS at 5-year follow-up)

The association between baseline covariates and daytime sleepiness at 5-year follow-up was estimated using (multiple) linear regression, 1) adjusting for baseline daytime sleepiness, and 2) additionally adjusting for age and sex.

Main analysis: Association between exposure (5-year weight change) and outcome (ESS at 5-year follow-up)

We assessed the relationship between 5-year weight change and daytime sleepiness at 5-year follow-up using multiple linear regression, adjusting for baseline level of daytime sleepiness, and in another model, additionally adjusting for the minimum set of available confounders identified through our DAG: age, sex, education, diabetes, poor night sleep, smoking status, weight, and use of antidepressants and benzodiazepines at baseline. We did not adjust for race because 97% of the included study sample were white. We also tested for exposure/sex interaction and exposure/baseline BMI categories (<25 kg/m^2, 25-29.9 kg/m^2, ≥30 kg/m^2) interaction. We considered exposure/sex interaction as previous studies suggested a substantial difference between men and women in the way of reporting of daytime sleepiness,[22,23] and in the strength of relationship between obesity and obstructive sleep apnea.[24] We tested exposure/baseline BMI interaction because we suspected differences in amount of weight change in individuals with different baseline BMI levels.

Under the assumption of no unmeasured confounding and a correctly specified model, the coefficients for exposure in these models estimate the causal effect of a 10 kg weight gain in 5 years on the ESS score at 5 years.

Mediation analysis

We individually assessed a set of potential mediators between 5-year weight change and daytime sleepiness at 5 years through a causal (counterfactual) mediation analysis approach outlined by VanderWeele.[25] We fitted one model for the outcome, and one model for the mediator; both using multiple least square linear regressions, as both outcome and mediator were continuous variables. This approach is similar to the product-of-coefficient approach popularized by Baron & Kenny,[26] but allowing for exposure-mediator interaction. Two levels of exposures are being compared at any one time; in this case we chose to compare the counterfactual outcomes under 0 kg weight change and 10 kg weight gain. Using the coefficients produced from the outcome and mediator models, the natural direct effect (NDE), natural indirect effect

(NIE), and total effect were estimated; out of which, the proportion mediated (NIE/total effect) was calculated. The total effect, NDE, NIE, and their confidence intervals, were estimated using PARAMED, a the STATA® macro.[27] Under the assumptions of no unmeasured confounding between 1) exposure and outcome, 2) exposure and mediator, and 3) mediator and outcome, as well as 4) no mediator-outcome confounder that is affected by exposure, the estimated NDE, NIE and TE can have causal interpretations.[25] Each potential mediator was assessed in separate models. We adjusted for baseline level of the mediator in each model, in addition to the exposure-outcome confounders adjusted for in the main analysis (age, sex, education, diabetes, poor night sleep, smoking status, weight, level of daytime sleepiness, and use of antidepressants and benzodiazapines at baseline). We did not identify any other exposure-mediator or mediator-outcome confounders that were not already included as exposure-outcome confounders.

Sensitivity analysis

To test the robustness of our main finding towards outliers, we repeated our main analysis using robust regression (MM estimation).[28] To test the robustness of the mediation analysis towards outliers, we removed data points that were both outliers (as identified through robust regression), and influential points (as identified through least square regression, Cook's D>4/sample size); and repeated the mediation analysis excluding them.

Subsequently, we assessed the consistency of the main analysis findings in other subsets of study sample and/or at other study time-points, listed below:

1. Supplementary analysis 1. Exposure: 2-year weight change; Outcome: daytime sleepiness at 2 years in study participants with complete data on exposure, minimum set of confounders, and outcome at baseline and 2-year follow-up (n=1,106)
2. Supplementary analysis 2. Exposure: 2-year weight change; Outcome: daytime sleepiness at 2 years in study participants with complete data of exposure, minimum set of confounders, and outcome at baseline, 2-year, and 5-year follow-up. (n=649)
3. Supplementary analysis 3. Exposure: 5-year weight change; Outcome: daytime sleepiness at 5 years in study participants with complete data of exposure, minimum set of confounders, and outcome at baseline, 2-year, and 5-year follow-up 2 (n=649)

We also tested the consistency of our findings from the mediation analysis, alongside supplementary analysis 3. We could not perform mediation analysis alongside supplementary analysis 1 and 2 because the potential mediators were not measured at 2-years follow-up.

We assessed the robustness of our findings by repeating our analyses in other subsets of study samples, and exposure and outcome measured at other follow-up time-points, instead using data-missing handling approaches, due to the large proportion of missing data (50%). In addition, it is likely that data were "missing not at random" (the missing-ness mechanism depends on non-observed data),[29] e.g. study participants were more likely to miss their appointments due to being excessively sleepy on the day, or because they had not been sleeping well.

Ethics

This study was approved by The Alfred Ethics Committee (project number 228/14) and by the Monash University Human Research Ethics Committee (project number CF14/2837 – 2014001567)

Results

Baseline characteristics, and levels of exposure and outcome

The study participants were on average 55 years old, 46% were female, the mean baseline BMI was 28 kg/m^2, and 25% had EDS. Compared to men, women were more likely to have lower education, weight, BMI, ESS scores, OAHI, RDI, and SF-36 physical and mental component score at baseline. They were also more likely to have longer objective sleep duration, worse sleep disturbance score, insomnia, used benzodiazepines and antidepressants, and less likely to be a current or former smoker at baseline (**Table 1**).

There was an average 5-year weight gain of 1.4 kg in the overall study sample, with no difference by sex. However, 5-year BMI gain was borderline significantly higher in women than men (**Table 1**). ESS score at 5-year was significantly higher in men than women (**Table 1**).

Attrition analysis

Study participants who were excluded due to incomplete data were less likely to report insomnia, and more likely to be younger, non-white, highly educated, a non-smoker, with shorter sleep duration, and had lower SF-36 mental component score than those with complete data (Table A.2 in the Supplement). There were no difference in 5-year weight change and 5-year ESS scores between those with complete and incomplete data.

Association between baseline covariates and exposure (5-year weight change)

In the age- and sex- adjusted model, younger age, shorter subjective sleep duration, better OAHI and RDI, lower BMI (categories), and use of benzodiazepines at baseline were associated with greater 5-year weight gain **(Table 2)**.

Association between baseline covariates and outcome (daytime sleepiness at 5-year follow-up)

After adjusting for age and sex, being male was associated with lower ESS scores at 5-year follow-up; whilst having higher weight and ESS scores at baseline were associated with higher ESS scores at 5-year follow-up. (**Table 3**).

Main Analysis: The relationship between 5-year weight change and daytime sleepiness at 5-year follow-up

Table 4 shows that daytime sleepiness worsens with weight gain. There was a significant interaction by sex; in which the relationship between weight change and daytime sleepiness was only significant in women (**Table 4**). Even though interaction by baseline categories of BMI, was not significant (p= 0.4), we chose to investigate the effect in the strata defined by baseline BMI, based on matter knowledge. We found that 5-year weight change and daytime sleepiness were significantly associated only in the normal weight group (0.72, 95%CI 0.16 – 1.27, p=0.01, N=397); but not in the overweight (0.19, 95%CI -0.25 to 0.63, p=0.4, N=567) or obese group (0.35, 95%CI -0.02 to 0.71, p=0.06, N=504).

Mediation analysis: The potential pathways between 5-year weight change and daytime sleepiness at 5-year follow up

Around one-fifth (18.1%) of the relationship between weight change and daytime sleepiness was mediated by OAHI at 5-year follow-up, and around one-sixth (16.1%) by physical health at 5-year follow-up, **Table 5a**. The mediating effect of RDI at 5-year follow-up was borderline significant (**Table 5a**), but with similar magnitude to OAHI (17.9%). We found significant exposure/mental health interaction of the total effect

(interaction term: -0.054, 95%CI -0.095 to -0.02, p=0.001); the effect of weight change on daytime sleepiness appeared to be more pronounced in those with poorer mental health. We did not detect any other significant exposure-mediator interaction. The effect mediated through objective and subjective sleep duration was negligible.

There was a further reduction in sample size, and to a different degree in each set of models, due to the different number of missing data for each mediator. The total effect remained fairly consistent in the models for the different mediators (**Table 5a**).

Similar results were found when the mediation analyses were performed only in women (**Table 5b**), although the mediating effects of OAHI and physical health became borderline significant.

Sensitivity analysis

We repeated the main analysis using robust regression (MM estimation) to assess the robustness of our findings towards outliers, and found similar estimates for the relationship between 5-year weight change and daytime sleepiness at 5 years (Table A.3 in the Supplement), although exposure/sex interaction became non-significant (p=0.3). The exposure/baseline BMI interaction remained non-significant (p=0.8). When the mediation analyses were repeated, excluding outlier and influential data, the indirect effect through OAHI at 5-year follow-up remained significant but the indirect effect of physical health disappeared (Table A.4a in the Supplement). In the women-only study sample, the indirect effect of OAHI became borderline significant, the indirect effect through RDI and physical health became significant and borderline significant respectively (Table A.4b).

In supplementary analysis 1, the association between (2-year) weight change and daytime sleepiness at (2-year) follow-up, the exposure/sex interaction (Table A.5a & b in the Supplement), and the absence of exposure/baseline BMI interaction (data not shown) remained evident.

In supplementary analysis 2, the association between (2-year) weight change and daytime sleepiness at (2-year) follow-up, became non-significant in the overall study sample, but remained significant in women only, with a significant exposure/sex interaction (Table A.6a & b in the Supplement). The exposure/baseline BMI interaction remained non-significant (data not shown).

In supplementary analysis 3. The association between (5-year) weight change and daytime sleepiness at (5-year) follow-up, the exposure/sex interaction (Table A.7a in the Supplement), and the absence of exposure/baseline BMI interaction (data not shown) remained evident. When repeated using robust regression, the association between (5-year) weight change and daytime sleepiness at (5-year) follow-up became non-significant in the overall sample, but remained borderline significant in women, despite no significant exposure/sex interaction (Table A.7b in the Supplement). The exposure/baseline BMI interaction remained non-significant (data not shown). The indirect effect of OAHI in the overall study sample or women only sample became non-significant, although the magnitude of proportion mediated in the overall study sample remained similar. The indirect effect of physical health remained significant in the overall study sample, but not significant in women only sample (Table A.8a & b in the Supplement).

Throughout the different sensitivity and supplementary analyses, we consistently found a relationship between weight gain and worse daytime sleepiness in women. We also consistently found mediation through measures of severity of obstructive sleep apnea, OAHI or RDI, and physical health (measured through short-form 36). Exposure/baseline BMI interaction was not significant in any of the analyses. On the other hand, exposure/mental health interaction was consistently found across the analyses.

Discussion

In this study, through a causal framework, we have consistently found evidence supporting an association between weight gain and worse daytime sleepiness that may be partly mediated by severity of obstructive sleep apnea. The relationship seemed to be more pronounced in women and those with poorer mental health.

A recent study by Fernandez et al[8], similarly found higher risk of incident EDS with weight gain, and remitted EDS with weight loss. Another recent longitudinal study by Theorel-Haglow et al.[30] found that baseline obesity is a significant predictor of incident EDS. Palm et al found that BMI increase, but not baseline BMI, was associated with incident EDS.[9] In these studies, EDS was measured through unvalidated questionnaires, asking one or two questions only. Our study arrives at a similar conclusion, using the Epworth Sleepiness Scale, a validated,[11,16] and widely-used tool to assess daytime sleepiness.[24]

It is well-known that obesity causes OSA; this can occur through many pathways, one of which involves the increased mechanical pressure on the upper airway from fat accumulation around the neck.[31] It is also known that individuals with OSA report EDS, likely due to disturbed night-time sleep. Therefore, for a long time it was believed that obesity-related EDS mainly occurs through OSA. However, other pathways linking obesity to EDS have been suggested, because 1) in individuals with and without OSA, the prevalence of EDS were approximately similar, 2) even though obesity is highly correlated with OSA, OSA is only weakly correlated with EDS, and 3) there is residual daytime sleepiness that cannot be removed with the treatment of OSA through continuous positive airway pressure.[12] It was hypothesised that obesity may influence EDS through other pathways, either directly through the release of pro-inflammatory cytokines, or indirectly through a range of obesity-related comorbidities that disturb night time sleep.[12] Our study aimed to test this hypothesis. We showed for the first time that OSA has a mediating role between weight change and daytime sleepiness, but the majority of the relationship may occur through other pathways was independent of OSA. Physical health, but not mental health or sleep duration, also had a significant mediating effect between weight change and daytime sleepiness. Future studies may test the mediating effect of more specific indicators of poor physical/mental health such as glucose level, clinical depression or inflammatory markers, to help better understand the relationship between weight change and daytime sleepiness.

Given that Newman et al. has shown a stronger relationship between obesity and obstructive sleep apnea in men than in women,[24] and previous studies have shown that men are more likely to report higher ESS score than women,[22,23] we expected to see a stronger relationship between weight change and daytime sleepiness in men than in women. However, our results showed that the relationship between weight change and daytime sleepiness was only evident in women, but not in men. The lack of association between weight change and daytime sleepiness in men is unclear. One possible explanation is that men were heavier at baseline, with weight at baseline negatively associated with degree of weight change. Another is the presence of other potential mediators such as obesity-related asthma, which only develops in women, but not in men. [8,32] However, this apparent difference requires further investigation.

In this study sample, even though baseline mental health did not predict 5-year weight change, or ESS at follow-up, it was an effect modifier in the relationship between weight change and daytime sleepiness. To our knowledge, no other studies have assessed the interaction between weight change and sex/mental health in their association with daytime sleepiness.

Strengths

The SHHS used the Epworth Sleepiness Scale, a validated,[11,16] and widely-used questionnaire to assess daytime sleepiness. The SHHS also measured a wide range of key metabolic, cardiovascular, sleep (both

objective through polysomnography and subjective through questionnaires), and lifestyle variables repeatedly over 5-years follow-up, which allowed us to adjust for a majority of the confounding factors we had identified through a directed acyclic graph approach and perform a mediation analysis of the effect of weight change and daytime sleepiness.

Although Fernandez et al.[8], Theorel-Haglow et al.,[30] and Palm et al.[9] found significant association between obesity/weight change and daytime sleepiness, the possibility of causal inference remained unclear, because the extent to which the assumption of "no unmeasured confounding" holds was not explicitly described. Our study made an additional contribution towards understanding the causal relationship between weight change and daytime sleepiness because we have clarified the conditions under which the identified associations can be causal, through the provision of our DAG, and the explicit statements of the assumptions made.

Limitations

To infer causation from associations in observational studies, a main and untestable assumption is that all confounders of the exposure/outcome relationship are measured ("no-unmeasured confounding"). In our analysis, we had adjusted for the majority of the confounders identified through our DAG, but not for the diagnosis of circadian-rhythm sleep-wake disorder, which was unavailable. Therefore, residual confounding cannot be ruled out. However, it is important to note that even if we had adjusted for every confounder identified through our DAG, the "no-unmeasured confounding" assumption is untestable. This is the main limitation in observational studies.[10] At the very least, the DAG that we displayed in this article provides a transparent view to how the potential confounders were considered and selected for our statistical models. Future studies may test the reproducibility of our findings by adjusting for similar confounders, as well as circadian-rhythm sleep-wake disorder.

In addition, to infer causation from association in observational studies, we also need to fulfil the criteria of "well-defined intervention".[10] This is always a problem for studies treating obesity or unintentional weight change as an exposure, because there is more than one way to achieve weight change, and the method through which weight change is achieved may have an independent effect on the study outcome. For instance, it might be that diet or physical activity, the most common mechanisms to lose weight, may affect daytime sleepiness directly, independently of weight change.

The temporal sequence cannot be determined for some of the variables measured at the 5-year follow-up. It is possible that higher daytime sleepiness causes weight gain, perhaps through reduced physical activity. Similarly for mediation analysis, because potential mediators and outcome were measured at the same time, at the 5-year follow up, we could not determine whether mediator occurred before outcome, or vice versa.

In this study, weight change was assessed as a continuum, involving both weight gain and weight loss. However, the distribution of weight change in this study sample was weighted towards weight gain. While we are confident with our conclusion on the association between weight gain and daytime sleepiness, the generalisability of our finding to the relationship between weight loss and daytime sleepiness is less certain. Supporting a continuous association, a recent meta-analysis on weight loss interventions has shown a dose-response relationship between the amount of weight loss and the degree of improvement in daytime sleepiness. [33] There is a high proportion of missing data in the SHHS (50%, mostly due to loss-to-follow-up); and therefore, risk of selection bias. Study participants with complete data at baseline and 5-year follow-up were more likely to be older, white, have lower education, smoke cigarettes, have insomnia, and had longer sleep duration and higher SF-36 mental score, than those excluded due to incomplete data. However, there was no difference in exposure and outcome levels in those with or without incomplete data (where data were available). Note that due to large sample sizes, small differences between groups are statistically

significant. Further, our finding on the association between weight change and daytime sleepiness, as well as results from mediation analysis, were consistent across a range of supplementary analyses in different subsets of the study sample. The study participants in the SHHS dataset were recruited from six different parent cohorts. The SHHS dataset made available through the National Sleep Research Resource did not provide information on which parent cohort each study participants came from; hence we were not able to adjust for potential clustering effect. The high variability we found in our analyses, may be partly explained by this.

Conclusion

Our study showed for the first time, that weight gain is associated with daytime sleepiness as assessed through the Epworth sleepiness scale, and that approximately one-fifth of this relationship occurs through obstructive sleep apnea, and approximately one-sixth through poor overall physical health. We described explicitly, the extent to which the assumptions of "no unmeasured confounding" and "well-defined intervention", may affect causal inference from our study findings. This provides further understanding of the causal pathway between weight change and daytime sleepiness, which may help in the management of obesity-related EDS. We recommend future studies test the reproducibility of our findings in a dataset with less missing data; and in the setting of weight loss interventions with amount of weight loss as a potential mediator, so problems with ill-defined intervention and temporal direction can be addressed. We also recommend the exploration of other potential mediators between obesity and EDS, such as inflammatory markers, or other obesity-related medical conditions (e.g. glucose level and clinical depression).

Conflicts of Interest

The authors have nothing to disclose.

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Table 1. Baseline characteristics, and levels of exposure and outcome in the primary study sample, n=1,468

Baseline covariates	Total	Men	Women	p-value
	N= 1,468	N= 679	N= 789	
DEMOGRAPHICS				
Age, years	55.3 (6.1)	55.6 (6.2)	55.1 (6.1)	0.1
Male, n(%)	679 (46.3)	-	-	-
Race, n(%)				
White	1,415 (96.4)	658 (96.9)	757 (95.9)	
Black	8 (0.5)	3 (0.4)	5 (0.6)	0.6
Others	45 (3.1)	18 (2.7)	27 (3.4)	
Education, n(%)				
<10 years	49 (3.3)	22 (3.2)	27 (3.4)	
10-15 years	759 (51.7)	322 (47.4)	437 (55.4)	0.01
>15 years	660 (45.0)	335 (49.3)	325 (41.2)	
ANTHROPOMETRIC MEASURES				
Weight, kg	81.5 (16.8)	90.1 (13.9)	74.1 (15.5)	<0.001
BMI, kg/m^2	28.4 (5.0)	29.0 (4.2)	27.9 (5.6)	<0.001
Normal weight (BMI 18.5-24.9)	397 (27.0)	22 (3.2)	27 (3.4)	
Overweight (BMI 25.0-29.9)	567 (38.6)	322 (47.4)	437 (55.4)	<0.001
Obese (BMI ≥ 30.0)	504 (34.3)	335 (49.3)	325 (41.2)	
SLEEP MEASURES				
ESS score, unit	7.8 (4.3)	8.3 (4.4)	7.5 (4.2)	<0.001
Subjective sleep duration, hrs	7.2 (1.0)	7.2 (1.0)	7.3 (1.0)	0.2
Objective sleep duration, min	376.5 (57.3)	368.7 (56.5)	383.3 (57.1)	<0.001
OAHI, events/hr	7.1 (10.8)	9.6 (12.5)	4.8 (8.6)	<0.001
RDI, events/hr	7.3 (11.3)	10.0 (13.2)	4.9 (8.7)	<0.001
Sleep disturbance, unit	9.2 (4.7)	8.5 (4.6)	9.8 (4.7)	<0.001
Insomnia, n(%)	426 (29.2)	158 (23.3)	268 (34.3)	<0.001
OTHER HEALTH MEASURES				
Diabetes, n(%)	59 (4.0)	30 (4.4)	29 (3.7)	0.5
Short-form 36				
Mental component score	53.6 (7.4)	54.1 (7.1)	53.2 (7.7)	0.02
Physical component score	50.1 (8.3)	50.6 (7.9)	49.7 (8.6)	0.049
Medications, n(%)				
Benzodiazepines	53 (3.6)	15 (2.2)	38 (4.8)	0.01
Antidepressants	120 (8.2)	28 (4.1)	92 (11.7)	<0.001
Smoking status, n(%)				
Never	648 (44.1)	240 (35.3)	408 (51.7)	<0.001
Former	171 (11.6)	89 (13.1)	82 (10.4)	

	Current	649 (44.2)	350 (51.5)	299 (37.9)	
EXPOSURE					
5-years weight change, kg		1.4 (6.3)	1.3 (5.9)	1.4 (6.6)	0.8
5-years BMI change, kg/m^2*		0.8 (2.3)	0.7 (2.0)	0.9 (2.5)	0.05
OUTCOME					
Mean ESS score at 5-years, unit		7.2 (4.1)	7.8 (4.2)	6.7 (4.0)	<0.001

*Not used in main analysisThe primary study sample refers to the subset of 1,468 participants with complete data on exposure, minimum set of confounders, and outcome at baseline and 5-year follow-up. Exposure refers to 5-year weight change; the minimum set of confounders include age, sex, education, diabetes, subjective sleep duration, sleep disturbance, smoking status, weight, level of daytime sleepiness and the use of antidepressants and benzodiazepines at baseline; outcome refers to daytime sleepiness at 5-year follow-up.

All data are presented as mean (standard deviation) for continuous variables and n (%) for categorical variables

Abbreviations: BMI, Body mass index; ESS, Epworth Sleepiness Scale; OAHI, Obstructive apnea-hypopnea index; RDI, Respiratory disturbance index.

Table 2. Association between baseline covariates and 5-year weight change, n=1,468

Baseline covariates	5-year weight change, kg (95%CI)					
	Unadjusted		p-value	Age- and sex-adjusted		p-value
DEMOGRAPHICS						
Age, years	-0.16	(-0.21 to -0.11)	<0.001	-0.16	(-0.21 to -0.11)	<0.001
Male	0.08	(-0.57 to 0.72)	0.8	0.00	(-0.64 to 0.63)	1.0
Race						
White		reference			reference	
Black	1.77	(-2.57 to 6.11)	0.03	1.42	(-2.88 to 5.72)	0.3
Others	2.39	(0.54 to 4.25)		1.31	(-0.56 to 3.18)	
Education						
<10 years	-0.57	(-2.38 to 1.24)		0.00	(-1.80 to 1.79)	
10-15 years		reference	0.7		reference	0.7
>15 years	-0.24	(-0.89 to 0.41)		-0.27	(-0.92 to 0.38)	
ANTHROPOMETRIC MEASURES						
Weight, kg	-0.02	(-0.04 to 0.00)	0.06	-0.02	(-0.04 to 0.00)	0.06
BMI, kg/m^2	-0.21	(-0.28 to -0.15)	<0.001	-0.21	(-0.27 to -0.14)	<0.001
Normal weight (BMI 18.5-24.9)		reference			reference	
Overweight (BMI 25.0-29.9)	-0.44	(-1.24 to 0.36)	<0.001	-0.34	(-1.14 to 0.46)	<0.001
Obese (BMI ≥ 30.0)	-1.80	(-2.61 to -0.98)		-1.60	(-2.43 to -0.78)	
SLEEP MEASURES						
ESS score, unit	-0.03	(-0.11 to 0.04)	0.4	-0.01	(-0.08 to 0.07)	0.8
Subjective sleep duration, hrs	-0.37	(-0.69 to -0.06)	0.02	-0.38	(-0.69 to -0.07)	0.02
Objective sleep duration, min	0.003	(-0.002 to 0.009)	0.2	0.001	(-0.004 to 0.007)	0.6
OAHI, events/hr	-0.05	(-0.08 to -0.02)	0.001	-0.05	(-0.08 to -0.02)	0.003
RDI, events/hr	-0.05	(-0.08 to -0.02)	0.001	-0.04	(-0.07 to -0.01)	0.004
Sleep disturbance, unit	0.01	(-0.05 to 0.08)	0.7	0.03	(-0.04 to 0.10)	0.4
Insomnia	-0.03	(-0.11 to 0.04)	0.40	-0.01	(-0.08 to 0.07)	0.8
OTHER HEALTH MEASURES						
Diabetes	-1.04	(-2.67 to 0.59)	0.2	-0.70	(-2.32 to 0.91)	0.4
Short-form 36						
Mental component score	-0.03	(-0.08 to 0.01)	0.1	-0.02	(-0.06 to 0.03)	0.5
Physical component score	0.03	(-0.01 to 0.07)	0.2	0.02	(-0.02 to 0.06)	0.4
Medications						
Benzodiazepines	1.64	(-0.08 to 3.35)	0.06	1.90	(0.20 to 3.60)	0.03
Antidepressants	1.37	(0.20 to 2.53)	0.02	1.14	(-0.03 to 2.31)	0.06
Smoking status						
Never		reference			reference	
Former	0.90	(-0.15 to 1.96)	0.1	0.82	(-0.22 to 1.87)	0.2
Current	-0.27	(-0.95 to 0.41)		-0.02	(-0.70 to 0.67)	

Abbreviations: BMI, Body mass index; ESS, Epworth Sleepiness Scale; OAHI, Obstructive apnea-hypopnea index; RDI, Respiratory disturbance index

Table 3. Association between baseline covariates and daytime sleepiness at 5-year follow-up, n=1,468

Baseline covariates	ESS at 5-year follow-up Beta coefficient (95% CI)					
	Unadjusted		p-value	Age- and sex-adjusted		p-value
DEMOGRAPHICS						
Age, years	-0.02	(-0.04 to 0.01)	0.2	-0.02	(-0.04 to 0.01)	0.2
Male	-0.49	(-0.79 to -0.19)	0.001	-0.50	(-0.80 to -0.19)	0.001
Race						
White		reference			reference	
Black	0.02	(-2.02 to 2.06)	0.6	0.02	(-2.01 to 2.06)	0.4
Others	-0.47	(-1.34 to 0.40)		-0.58	(-1.47 to 0.31)	
Education						
<10 years	-0.25	(-1.10 to 0.60)		-0.20	(-1.05 to 0.65)	
10-15 years		reference	0.7		reference	0.6
>15 years	-0.12	(-0.42 to 0.19)		-0.16	(-0.47 to 0.15)	
ANTHROPOMETRIC MEASURES						
Weight, kg	0.017	(0.007 to 0.026)	<0.001	0.012	(0.002 to 0.023)	0.02
BMI, kg/m^2	0.032	(0.002 to 0.062)	0.04	0.028	(-0.002 to 0.058)	0.07
Normal weight (BMI 18.5-24.9)		Reference			reference	
Overweight (BMI 25.0-29.9)	0.17	(-0.21 to 0.54)	0.2	0.09	(-0.30 to 0.47)	0.3
Obese (BMI ≥ 30.0)	0.37	(-0.02 to 0.76)		0.30	(-0.09 to 0.70)	
SLEEP MEASURES						
ESS score, unit	0.67	(0.64 to 0.71)	<0.001	0.67	(0.63 to 0.70)	<0.001
Subjective sleep duration, hrs	0.03	(-0.12 to 0.17)	0.7	0.03	(-0.11 to 0.18)	0.6
Objective sleep duration, hrs	0.001	(-0.002 to 0.003)	0.6	0.001	(-0.002 to 0.004)	0.5
OAHI, events/hour	0.01	(-0.00 to 0.02)	0.2	0.01	(-0.01 to 0.02)	0.5
RDI, events/hour	0.009	(-0.004 to 0.023)	0.2	0.006	(-0.008 to 0.019)	0.4
Sleep disturbance, unit	-0.02	(-0.05 to 0.02)	0.4	-0.01	(-0.04 to 0.03)	0.7
Insomnia	-0.19	(-0.52 to 0.14)	0.3	-0.14	(-0.60 to 0.33)	0.6
OTHER HEALTH MEASURES						
Diabetes	-0.15	(-0.91 to 0.62)	0.7	-0.13	(-0.90 to 0.63)	0.7
Short-form 36, unit						
Mental component score	-0.01	(-0.03 to 0.01)	0.3	-0.01	(-0.03 to 0.01)	0.3
Physical component score	-0.01	(-0.03 to 0.01)	0.3	-0.01	(-0.03 to 0.01)	0.2
Medications						
Benzodiazepines	-0.77	(-1.57 to 0.03)	0.06	-0.66	(-1.46 to 0.15)	0.1
Antidepressants	0.27	(-0.28 to 0.81)	0.3	0.38	(-0.18 to 0.93)	0.2
Smoking status						
Never		reference			reference	
Former	0.22	(-0.28 to 0.71)	0.6	0.13	(-0.36 to 0.63)	0.6
Current	-0.05	(-0.37 to 0.27)		-0.11	(-0.43 to 0.22)	

Abbreviations: BMI, Body mass index; ESS, Epworth Sleepiness Scale; OAHI, Obstructive apnea-hypopnea index; RDI, Respiratory disturbance index

Table 4. The relationship between 5-year weight change and daytime sleepiness at 5-year follow-up, overall and stratified by sex

	Total population n=1,468				Men n=679				Women n=789				p for sex interaction
	ESS at 5-year follow-up unit (95%CI)			p	ESS at 5-year follow-up unit (95%CI)			p	ESS at 5-year follow-up unit (95%CI)			p	
Adjusted for baseline ESS													
5-year weight change, 10 kg	0.33	(0.09 to	0.57)	0.01	0.00	(-0.39 to	0.40)	1.0	0.54	(0.25 to	0.84)	<0.001	0.03
Adjusted for baseline ESS and other confounders in the minimum adjustment set													
5-year weight change, 10kg	0.36	(0.12 to	0.61)	0.004	0.06	(-0.35 to	0.46)	0.8	0.55	(0.25 to	0.86)	<0.001	0.02

Abbreviations: ESS, Epworth sleepiness scale

The minimum set of confounders includes age, sex, education, diabetes, subjective sleep duration, sleep disturbance, smoking status, weight, level of daytime sleepiness and the use of antidepressants and benzodiazepines at baseline.

Table 5. Mediation analysis between 5-year weight change and ESS at 5-year follow-up, in a) the overall study sample (n=1,468) and b) women only (n=789)

a)

Mediators	n	P (Exposure-Mediator interaction)	ESS at 5-year follow-up, coefficient (95%CI)			% Mediated
			Natural direct effect	Natural indirect effect	Total effect	
OAHI at 5-year follow-up	1,115	0.4	0.330 (0.034 to 0.626)*	0.073 (0.001 to 0.145)*	0.403 (0.119 - 0.687)*	18.1
RDI at 5-year follow-up	1,115	0.3	0.328 (0.032 to 0.625)*	0.072 (-0.001 to 0.625)#	0.400 (0.116 to 0.684)*	17.9
Mental health at 5-year follow-up	1,278	0.001	0.415 (0.158 - 0.673)*	-0.044 (-0.104 to 0.015)	0.371 (0.109 - 0.632)*	-
Physical health at 5-year follow-up	1,278	0.07	0.256 (-0.007 to 0.519)#	0.049 (0.003 to 0.096)*	0.305 (0.042 - 0.568)*	16.1
Objective sleep duration at 5-yearfollow-up	1,115	0.8	0.403 (0.121 - 0.685)*	0.002 (-0.009 to 0.014)	0.405 (0.122 - 0.687)*	0.5
Subjective sleep duration at 5-year follow-up	1,393	0.7	0.374 (0.124 - 0.624)*	0.005 (-0.010 to 0.020)	0.379 (0.129 - 0.630)*	1.4

b)

Mediators	n	P (Exposure-Mediator interaction)	ESS at 5-year follow-up, coefficient (95%CI)			% Mediated
			Natural direct effect	Natural indirect effect	Total effect	
OAHI at 5-year follow-up	596	0.08	0.438 (0.047 to 0.829)*	0.079 (-0.005 to 0.164)#	0.517 (0.141 - 0.893)*	15.3
RDI at 5-year follow-up	596	0.2	0.432 (0.040 to 0.823)*	0.076 (-0.008 to 0.159)#	0.507 (0.131 - 0.883)*	14.9
Mental health at 5-year follow-up	698	0.01	0.669 (0.351 - 0.987)*	-0.037 (-0.109 to 0.036)	0.632 (0.309 - 0.955)*	-
Physical health at 5-year follow-up	698	0.5	0.505 (0.172 - 0.839)*	0.055 (-0.007 to 0.117)#	0.561 (0.237 - 0.885)*	9.8
Objective sleep duration at 5-year follow-up	596	0.2	0.552 (0.187 - 0.917)*	0.002 (-0.023 to 0.027)	0.554 (0.188 - 0.920)*	0.4
Subjective sleep duration at 5-year follow-up	750	0.5	0.571 (0.264 - 0.879)*	0.004 (-0.021 to 0.028)	0.575 (0.266 - 0.884)*	0.01

* Indicates p<0.05

# Indicates p value between 0.05 and 0.1

$This analysis involves comparison of two levels of exposure, 0 weight change and 10 kg weight gain.

The models adjust for: age, sex, education, diabetes, subjective sleep duration, sleep disturbance, smoking status, weight, level of daytime sleepiness, and use of antidepressants and benzodiazepines at baseline; as well as baseline levels of the mediator, if not already included. RDI and OAHI were not mutually adjusted. Objective and subjective sleep duration were not mutually adjusted

Only one potential mediator was considered at any one time. Further reduction in sample size was due to missing data on mediators.

Abbreviations: ESS, Epworth Sleepiness Scale; OAHI, Obstructive apnea-hypopnea index; RDI, Respiratory disturbance index

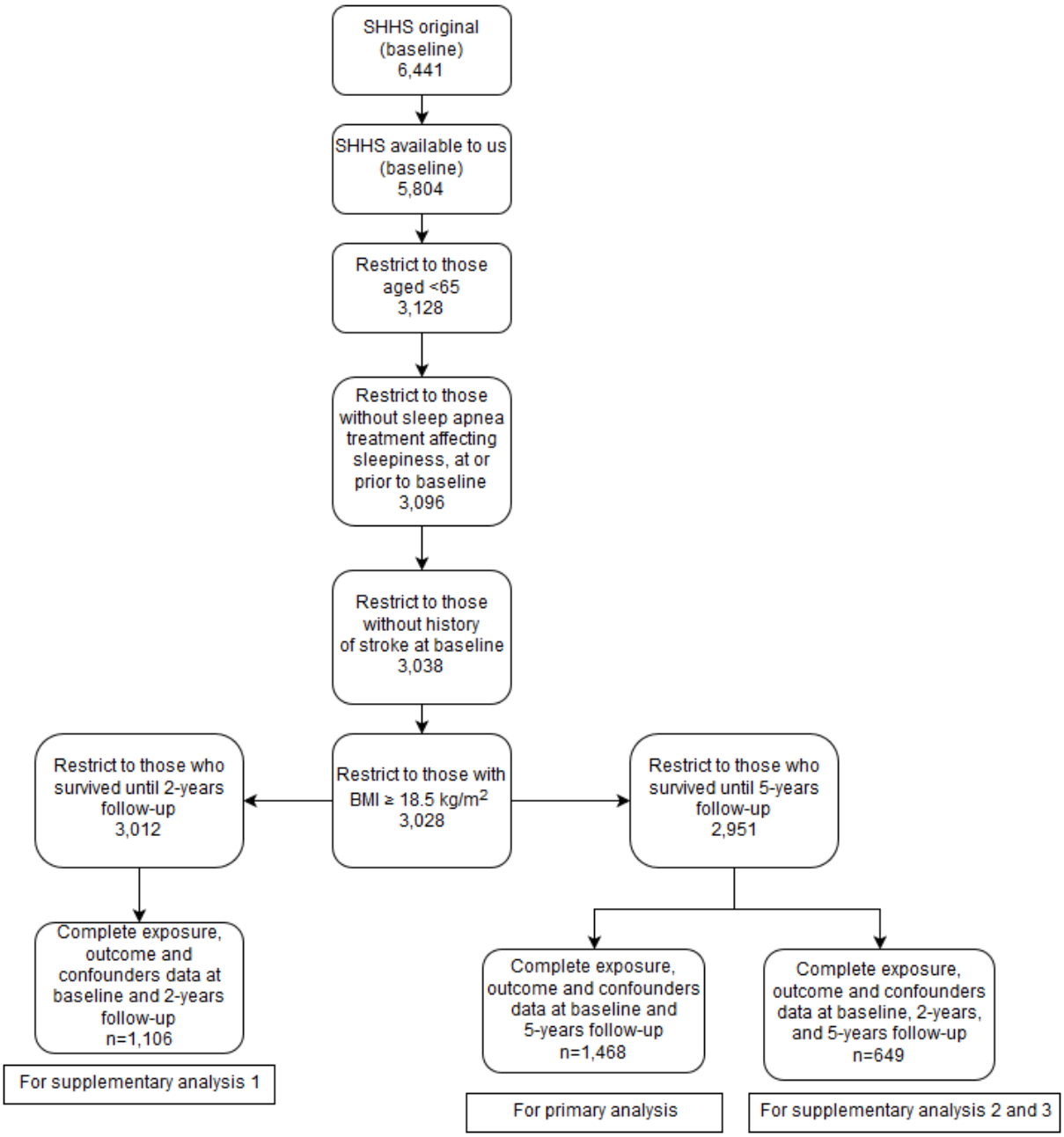

Figure 1. Flowchart summarizing the Sleep Heart Health Study participants

Abbreviations: BMI, Body mass index; SHHS, Sleep Heart Health Study

Outcome refers to daytime sleepiness or Epworth Sleepiness Scale scores at 2-years or 5-years follow-up, exposure refers to 2-years or 5-years weight change, confounders refer to the minimum adjustment set identified through the causal diagram (Fig. A.1 in the Supplement, includes age, sex, education, diabetes status, subjective sleep duration, sleep disturbance, smoking status, weight, level of daytime sleepiness, and use of antidepressants and benzodiazepines at baseline).

Supplementary Appendix

The relationship between weight change and daytime sleepiness: The Sleep Heart Health Study

Winda L. NG, Liliana Orellana, Jonathan E. Shaw, Evelyn Wong, Anna Peeters

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Table A.1 Measurement and availability of exposure, mediator, outcome and covariates

Variables	Measured at			Measurement tool/method
	Baseline	2-years follow-up	5-years follow-up	
Main measures				
Weight	X	X	X	Weight was measured at all three time-points in light clothes on a portable scale and height was obtained from parent cohorts. Body mass index was calculated as weight (kg)/height $(m)^2$
Daytime sleepiness	X	X	X	Daytime sleepiness was assessed through Epworth Sleepiness Scale, a self-reported questionnaire with total score ranging from 0 to 24.
Mediators				
Objective sleep duration	X		X	Assessed from 'total sleep time' during home-based polysomnography examination. A portable system was used (PS-2 System; Compumedics Limited, Abbotsford, Victoria, Australia).
Obstructive apnea-hypopnea index	X		X	Defined as total number of obstructive apnea and hypopnea events with ≥4% oxyhaemoglobin desaturation index, divided by total sleep time. Apnea and hypopnea events were assessed through polysomnography, using a portable system (PS-2 System; Compumedics Limited, Abbotsford, Victoria, Australia).
Respiratory disturbance index	X		X	Defined as total number of apnea and hypopnea events with ≥4% oxyhaemoglobin desaturation index, divided by total sleep time. Apnea and hypopnea events were assessed through polysomnography, using a portable system (PS-2 System; Compumedics Limited, Abbotsford, Victoria, Australia).

Smoking status	X		X	Assessed through health interview (baseline) or questionnaire on sleep habit (follow-up 2)
Self-reported sleep diagnosis and symptoms				Assessed through questionnaire on sleep habits and lifestyle.
Sleep duration	X	X	X	Reported in number of hours and minutes
Sleep disturbance	X			This involves the likelihood of being awakened by coughing/wheezing, chest pain/tightness, shortness of breath, sweats or hot flashes, noise in surroundings, pain in joints, muscles or back, heartburn/indigestion, leg cramps/jerks, need to go to bathroom. Total score ranges from 0 to 36
Undertaking treatment for sleep apnea	X	X	X	This includes use of continuous positive airway pressure, oxygen therapy, undertaking surgery and weight loss intervention. Information on continuous positive airway pressure was not collected at follow-up
(Symptoms of) Insomnia	X	X	X	This involves "have trouble falling asleep", "wake up during the night and have difficulty getting back to sleep", "wake up too early in the morning and be unable to get back to sleep"; each rated on five-point Likert scales. Insomnia is defined as scoring "often" or "always" on any of the three problems.
Feeling unrested	X	X	X	Measured on five-point Likert scale
Daytime sleepiness	X		X	Measured on five-point Likert scale (separate to Epworth Sleepiness Scale)
Sleeping pills	X	X	X	Measured on five-point Likert scale (frequency)
Mental Health	X		X	Assessed through short-form 36, which involves eight domains of

Physical Health	X	X	measurement: physical functioning, role limitations due to physical problems, role limitations due to emotional problems, mental health, energy and vitality, pain, and general perception of health. The eight domains were summarised to form the mental component score (used as mental health indicator in this study) and the physical component score (used as physical health indicator in this study).
Diabetes status	X	X	Assessed through questionnaire on history of diabetes diagnosed by physician and use of diabetes medication
Use of antidepressants	X	X	Assessed through questionnaire
Use of benzodiazepines	X	X	Assessed through questionnaire

All questionnaires from Sleep Heart Study are available for download from the study website[34] as well as from the National Sleep Research Resource website[14]

Table A.2. Comparison of baseline characteristics, and levels of exposure and outcome, between eligible study participants with and without complete data on exposure, minimum set of confounders and outcome in the primary dataset

Baseline characteristics	with complete exposure, confounders and outcome data		with incomplete exposure and/or confounders and/or outcome data		P-value
	N	Mean (SD) or n(%)	N	Mean (SD) or n(%)	
DEMOGRAPHICS					
Age, years	1,468	55.3 (6.1)	1,483	53.4 (6.9)	<0.001
Male, n(%)	1,468	679 (46.3)	1,483	702 (47.3)	0.6
Race, n(%)					
White		1,415 (96.4)		980 (66.1)	
Black	1,468	8 (0.5)	1,483	223 (15.0)	<0.001
Others		45 (3.1)		280 (18.9)	
Education, n(%)					
<10 years		49 (3.3)		44 (4.1)	
10-15 years	1,468	759 (51.7)	1,086	469 (43.2)	<0.001
>15 years		660 (45.0)		573 (52.8)	
ANTHROPOMETRIC MEASURES					
Weight, kg	1,468	81.5 (16.8)	1,480	81.4 (18.1)	0.9
BMI, kg/m^2	1,468	28.4 (5.0)	1,449	28.6 (5.5)	0.4
Normal weight (BMI 18.5-24.9)		397 (27.0)		399 (27.5)	
Overweight (BMI 25.0-29.9)	1,468	567 (38.6)	1,449	589 (40.6)	0.3
Obese (BMI ≥ 30.0)		504 (34.3)		461 (31.8)	
SLEEP MEASURES					
ESS score, unit	1,468	7.8 (4.3)	1,374	8.1 (4.6)	0.1
Subjective sleep duration, hrs	1,468	7.2 (1.0)	1,429	7.1 (1.1)	<0.001
Objective sleep duration, min	1,468	376.5 (57.3)	1,483	364.1 (64.1)	<0.001
OAHI, events/hr	1,468	7.1 (10.8)	1,483	7.7 (12.9)	0.1
RDI, events/hr	1,468	7.3 (11.3)	1,483	7.9 (13.1)	0.2
Sleep disturbance, unit	1,468	9.2 (4.7)	1,289	9.3 (5.3)	0.5
Insomnia, n(%)	1,459	426 (29.2)	1,435	44 (3.1)	0.047
OTHER HEALTH MEASURES					
Diabetes, n(%)	1,399	60 (4.3)	1,483	68 (4.6)	0.4
Short-form 36					
Mental component score	1,313	53.6 (7.4)	1,324	51.6 (8.6)	<0.001
Physical component score	1,313	50.1 (8.3)	1,324	49.5 (9.1)	0.09
Medications, n(%)					
Benzodiazepines	1,468	1,415 (96.4)	1,470	1,415 (96.3)	0.78
Antidepressants	1,468	1,348 (91.8)	1,483	1,415 (95.4)	0.44

Smoking status					
	Never	648 (44.1)		733 (50.4)	
	Former 1,468	171 (11.6)	1,453	186 (12.8)	<0.001
	Current	649 (44.2)		534 (36.8)	
EXPOSURE					
5-years weight change	1,468	1.4 (6.3)	418	1.6 (6.4)	0.5
5-years BMI change*	1,468	0.8 (2.3)	418	0.9 (2.7)	0.5
OUTCOME					
ESS score at 5-years, unit	1,468	7.2 (4.1)	629	7.4 (4.2)	0.4

*Not used in main analysis

Exposure refers to 5-year weight change; the minimum set of confounders includes age, sex, education, diabetes, subjective sleep duration, sleep disturbance, smoking status, weight, level of daytime sleepiness and the use of antidepressants and benzodiazepines at baseline; outcome refers to daytime sleepiness at 5-year follow-up. The primary dataset includes those with complete measures of exposure, confounders and outcome, n=1,468.

Abbreviations: BMI, Body mass index; ESS, Epworth Sleepiness Scale; OAHI, Obstructive apnea-hypopnea index; RDI, Respiratory disturbance index

Table A.3. Sensitivity analysis for the main analysis, assessing the relationship between 5-year weight change and daytime sleepiness at 5-year follow-up, using robust regression (MM estimation)

	Total population n=1,468				Men n=679				Women n=789				p for sex interaction
	ESS at 5-years follow-up unit (95%CI)			p	ESS at 5-years follow-up unit (95%CI)			p	ESS at 5-years follow-up unit (95%CI)			p	
Adjusted for baseline ESS													
5-year weight change, 10 kg	0.24	(-0.00 to	0.49)	0.05	0.08	(-0.35 to	0.50)	0.7	0.32	(0.03 to	0.61)	0.03	0.3
Adjusted for baseline ESS and other confounders in the minimum adjustment set													
5-year weight change, 10 kg	0.29	(0.03 to	0.54)	0.03	0.15	(-0.29 to	0.59)	0.5	0.35	(0.02 to	0.68)	0.04	0.3

The minimum set of confounders include age, sex, education, diabetes, subjective sleep duration, sleep disturbance, smoking status, level of daytime sleepiness, weight, and the use of antidepressants and benzodiazepines at baseline. In analysis of the total population (n=1,468), the minimum set of confounders also includes sex.

Abbreviations: ESS, Epworth sleepiness scale

Table A.4. Sensitivity analysis for the mediation analysis between 5-year weight change and daytime sleepiness at 5-year follow-up, excluding influential observations, in a) the overall study sample (n=1,468) and b) women only (n=789)

a)

Mediators	n	P (Exposure-Mediator interaction)	ESS at 5-year follow-up, coefficient (95%CI)			% Mediated
			Natural direct effect	Natural indirect effect	Total effect	
OAHI at 5-year follow-up	1,018	0.3	0.101 (-0.198 to 0.399)	0.096 (0.001 to 0.188)*	0.195 (-0.092 to 0.482)	48.4
RDI at 5-year follow-up	1,017	0.3	0.079 (-0.219 to 0.378)	0.081 (-0.005 to 0.167)#	0.161 (-0.128 to 0.449)	50.5
Mental health at 5-year follow-up	1,152	0.3	0.160 (-0.093 to 0.413)	-0.010 (-0.048 to 0.028)	0.150 (-0.105 to 0.404)	-
Physical health at 5-year follow-up	1,169	0.1	0.171 (-0.078 to 0.420)	0.029 (-0.006 to 0.065)	0.200 (-0.049 to 0.450)	14.5
Objective sleep duration at 5-year follow-up	1,033	0.3	0.173 (-0.089 to 0.434)	-0.10 (-0.035 to 0.153)	0.163 (-0.101 to 0.427)	-
Subjective sleep duration at 5-year follow-up	1,290	0.3	0.248 (0.008 to 0.487)*	0.000 (-0.001 to 0.002)	0.248 (0.008 to 0.487)*	0.02

b)

Mediators	n	P (Exposure-Mediator interaction)	ESS at 5-year follow-up, coefficient (95%CI)			% Mediated
			Natural direct effect	Natural indirect effect	Total effect	
OAHI at 5-year follow-up	495	0.09	0.121 (-0.278 to 0.519)	0.097(-0.000 to 0.193)#	0.217 (-0.173 to 0.608)	44.5
RDI at 5-year follow-up	546	0.09	0.162 (-0.220 to 0.543)	0.092 (0.002 to 0.182)*	0.253 (-0.116 to 0.623)	36.2
Mental health at 5-year follow-up	623	0.2	0.260 (-0.063 to 0.582)	-0.016 (-0.083 to 0.051)	0.244 (-0.082 to 0.570)	-
Physical health at 5-year follow-up	627	0.5	0.339 (0.02 to 0.654)*	0.045 (-0.020 to 0.109)#	0.384 (0.072 to 0.696)*	11.7
Objective sleep duration at 5-year follow-up	542	0.9	0.325 (-0.021 to 0.670)#	0.001 (-0.011 to 0.014)	0.326 (-0.018 to 0.670)#	0.4
Subjective sleep duration at 5-year follow-up	692	0.2	0.316 (0.015 to 0.616)*	-0.000 (-0.006 to 0.006)	0.316 (0.015 to 0.616)*	-

* Indicates p<0.05

# Indicates p value between 0.05 and 0.1

As Table 5 in the main text, this analysis involves comparison of two levels of exposure, 0 weight change and 10 kg weight gain, in women.
The difference with table 5 is the exclusion of data points that are both an outlier (identified through robust regression (MM estimation)), and an influential point (Cook's D > 4/n), in the current analysis.
The above models adjusted for age, sex, education, diabetes, subjective sleep duration, sleep disturbance, smoking status, weight, level of daytime sleepiness, use of antidepressants and benzodiazepines, and the level of the respective mediators at baseline. RDI and OAHI were not mutually adjusted. Subjective and objective sleep duration were not mutually adjusted.
Abbreviations: ESS, Epworth Sleepiness Scale; OAHI, Obstructive apnea-hypopnea index; RDI, Respiratory disturbance index

Table A.5 Supplemental Analysis 1. The relationship between 2-year weight change and daytime sleepiness at 2-year follow-up, in the subset of study sample with complete data at baseline and 2-year follow-up, n=1,106; using (a) least square regression, and (b) robust regression (MM estimation)

a)	Total population n=1,106			Men n=532			Women n=574			p for sex interaction
	ESS at 2-year follow-up unit (95%CI)		p	ESS at 2-year follow-up unit (95%CI)		p	ESS at 2-year follow-up unit (95%CI)		p	
Adjusted for baseline ESS										
2-year weight change, 10 kg	0.45	(0.15 to 0.76)	0.004	-0.02	(-0.48 to 0.44)	0.9	0.90	(0.49 to 1.30)	<0.001	0.01
Adjusted for baseline ESS and other confounders in the minimum adjustment set										
2-year weight change, 10 kg	0.43	(0.12 to 0.74)	0.01	-0.04	(-0.50 to 0.43)	0.9	0.87	(0.45 to 1.29)	<0.001	0.004

b)	Total population n=1,106			Men n=532			Women n=574			p for sex interaction
	ESS at 2-year follow-up unit (95%CI)		p	ESS at 2-year follow-up unit (95%CI)		p	ESS at 2-year follow-up unit (95%CI)		p	
Adjusted for baseline ESS										
2-year weight change, 10 kg	0.34	(0.04 to 0.64)	0.03	0.00	(-0.43 to 0.44)	1.0	0.64	(0.19 to 1.09)	0.01	0.04
Adjusted for baseline ESS and other confounders in the minimum adjustment set										
2-year weight change, 10 kg	0.31	(0.00 to 0.62)	0.05	-0.01	(-0.43 to 0.41)	1.0	0.62	(0.17 to 1.08)	0.01	0.03

Exposure: 2-year weight change; Outcome: daytime sleepiness at 2-year in study participants with complete data of exposure, minimum set of confounders, and outcome at baseline and 2-year follow-up (n=1,106)

The minimum set of confounders include age, sex, education, race, baseline diabetes status, subjective sleep duration, sleep disturbance, smoking status, weight, level of daytime sleepiness, and use of antidepressants and benzodiazepines at baseline.

Abbreviations: ESS, Epworth sleepiness scale

Table A.6. Supplementary Analysis 2. The relationship between 2-year weight change and daytime sleepiness at 2-year follow-up, in the subset of study sample with complete data at baseline, 2-year, and 5-year follow-up, n=649; using (a) least square regression, and (b) robust regression (MM estimation)

a)	Total population n=649			Men n=297			Women n=352			p for sex interaction
	ESS at 2-year follow-up unit (95%CI)		p	ESS at 2-year follow-up unit (95%CI)		p	ESS at 2-year follow-up unit (95%CI)		p	
Adjusted for baseline ESS										
2-year weight change, 10 kg	0.31	(-0.12 to 0.73)	0.2	-0.30	(-0.99 to 0.40)	0.4	0.70	(0.17 to 1.23)	0.01	0.02
Adjusted for baseline ESS and other confounders in the minimum adjustment set										
2-years weight change, 10 kg	0.27	(-0.17 to 0.70)	0.2	-0.30	(-1.02 to 0.41)	0.4	0.66	(0.12 to 1.20)	0.02	0.02

b)	Total population n=649			Men n=297			Women n=352			p for sex interaction
	ESS at 2-year follow-up unit (95%CI)		p	ESS at 2-year follow-up unit (95%CI)		p	ESS at 2-year follow-up unit (95%CI)		p	
Adjusted for baseline ESS										
2-year weight change, 10 kg	0.18	(-0.29 to 0.65)	0.4	-0.45	(-1.11 to 0.21)	0.2	0.56	(0.07 to 1.05)	0.03	0.01
Adjusted for baseline ESS and minimum set of covariates										
2-year weight change, 10 kg	0.19	(-0.29 to 0.67)	0.4	-0.43	(-1.15 to 0.28)	0.2	0.57	(0.01 to 1.13)	0.05	0.02

Exposure: 2-year weight change; Outcome: daytime sleepiness at 2-year in study participants with complete data of exposure, minimum set of confounders, and outcome at baseline, 2-year, and 5-year follow-up. (n=649)

The minimum set of confounders include age, sex education, diabetes status, subjective sleep duration, sleep disturbance, smoking status, weight, level of daytime sleepiness and use of antidepressants and benzodiazepines at baseline.

Abbreviations: ESS, Epworth sleepiness scale

Table A.7. Supplementary Analysis 3. The relationship between 5-year weight change and daytime sleepiness at 5-year follow-up, in the subset of study sample with complete data at baseline, 2-year, and 5-year follow-up, n=649; using (a) least square regression, (b) robust regression (MM estimation)

a)	Total population n=649				Men n=297				Women n=352				p for sex interaction
	ESS at 5-year follow-up unit (95%CI)			p	ESS at 5-year follow-up unit (95%CI)			p	ESS at 5-year follow-up unit (95%CI)			p	
Adjusted for baseline ESS													
5-year weight change, kg	0.52	(0.15 to	0.89)	0.01	0.04	(-0.59 to	0.66)	0.9	0.81	(0.35 to	1.27)	0.001	0.05
Adjusted for baseline ESS and other confounders in the minimum adjustment set													
5-year weight change, 10 kg	0.50	(0.11 to	0.88)	0.01	0.03	(-0.61 to	0.67)	0.9	0.83	(0.36 to	1.31)	0.001	0.05

b)	Total population n=649				Men n=297				Women n=352				p for sex interaction
	ESS at 5-year follow-up unit (95%CI)			p	ESS at 5-yeas follow-up unit (95%CI)			p	ESS at 5-year follow-up unit (95%CI)			p	
Adjusted for baseline ESS													
5-year weight change, 10 kg	0.16	(-0.27 to	0.58)	0.5	-0.20	(-0.99 to	0.59)	0.6	0.31	(-0.19 to	0.81)	0.2	0.2
Adjusted for baseline ESS and other confounders in the minimum adjustment set													
5-year weight change, 10 kg	0.19	(-0.27 to	0.65)	0.4	-0.12	(-0.95 to	0.70)	0.8	0.46	(-0.06 to	0.98)	0.08	0.2

Exposure: 5-year weight change; Outcome: daytime sleepiness at 5-year in study participants with complete data of exposure, minimum set of confounders, and outcome at baseline, 2-year, and 5-year follow-up 2 (n=649)

The minimum set of confounders included age, sex, education, diabetes, subjective sleep duration, sleep disturbance, smoking status, weight, daytime sleepiness, and use of antidepressants and benzodiazepines at baseline.

Abbreviations: ESS, Epworth sleepiness scale

Table A.8. Mediation analysis between 5-year weight change and daytime sleepiness at 5-year follow-up, in the subset of study sample with complete data at baseline, 2-year, and 5-year follow-up; a) overall (n=649) and b) women only (n=352)

a)

Mediators	n	P (Exposure-Mediator interaction)	ESS at 5-years follow-up, coefficient (95%CI)			% Mediated
			Natural direct effect	Natural indirect effect	Total effect	
OAHI at 5-year follow-up	454	0.7	0.402 (-0.057 to 0.862)[#]	0.057 (-0.041 to 0.155)	0.459 (0.015 – 0.903)*	12.4
RDI at 5-year follow-up	454	0.7	0.404 (-0.056 to 0.864)[#]	0.058 (-0.046 to 0.161)	0.462 (0.018 - 0.905)*	12.5
Mental health at 5-year follow-up	638	0.001	0.519 (0.126 - 0.913)*	-0.032 (-0.146 to 0.081)	0.487 (0.083 - 0.891)*	-
Physical health at 5-year follow-up	638	0.04	0.373 (-0.025 to 0.771)[#]	0.103 (0.012 to 0.193)*	0.476 (0.077 - 0.875)*	21.6
Objective sleep duration at 5-year follow-up	454	0.1	0.435 (0.000 - 0.870)[#]	0.076 (-0.027 to 0.179)	0.512 (0.069 - 0.955)*	14.9
Subjective sleep duration at 5-year follow-up	647	0.8	0.475 (0.091 - 0.859)*	0.020 (-0.020 to 0.061)	0.495 (0.109 - 0.882)*	4.13

b)

Mediators	N	P (Exposure-Mediator interaction)	ESS at 5-years follow-up, coefficient (95%CI)			% Mediated
			Natural direct effect	Natural indirect effect	Total effect	
OAHI at 5-year follow-up	244	0.6	0.849 (0.249 to 1.450)*	0.051 (-0.044 to 0.146)	0.901 (0.311 - 1.490)*	5.7
RDI at 5-year follow-up	244	0.6	0.851 (0.249 to 1.453)*	0.443 (-0.044 to 0.133)	0.895 (0.304 - 1.486)*	4.9
Mental health at 5-year follow-up	348	0.03	0.891 (0.450 - 1.372)*	-0.008 (-0.136 to 0.120)	0.883 (0.390 - 1.376)*	-
Physical health at 5-year follow-up	348	0.3	0.774 (0.273 - 1.275)*	0.099 (-0.022 to 0.219)	0.872 (0.384 - 1.360)*	11.3
Objective sleep duration at 5-year follow-up	244	0.01	0.860 (0.298 - 1.421)*	0.120 (-0.083 to 0.322)	0.979 (0.396 - 1.562)*	12.2
Subjective sleep duration at 5-year follow-up	350	0.9	0.791 (0.301 - 1.281)*	0.040 (-0.039 to 0.120)	0.831 (0.330 - 1.333)*	4.8

* Indicates p<0.005

[#] Indicates p value between 0.05 and 0.1

[$]This analysis involves comparison of two levels of exposure, 0 weight change and 10 kg weight gain.

The models adjust for: age, sex, education, diabetes, subjective sleep duration, sleep disturbance, smoking status, weight, level of daytime sleepiness, and use of antidepressants and benzodiazepines at baseline; as well as baseline levels of the mediator, if not already included. RDI and OAHI were not mutually adjusted. Objective and subjective sleep duration were not mutually adjusted.
Only one potential mediator was considered at any one time. Further reduction in sample size was due to missing data on mediators.
Abbreviations: ESS, Epworth Sleepiness Scale; OAHI, Obstructive apnea-hypopnea index; RDI, Respiratory disturbance index

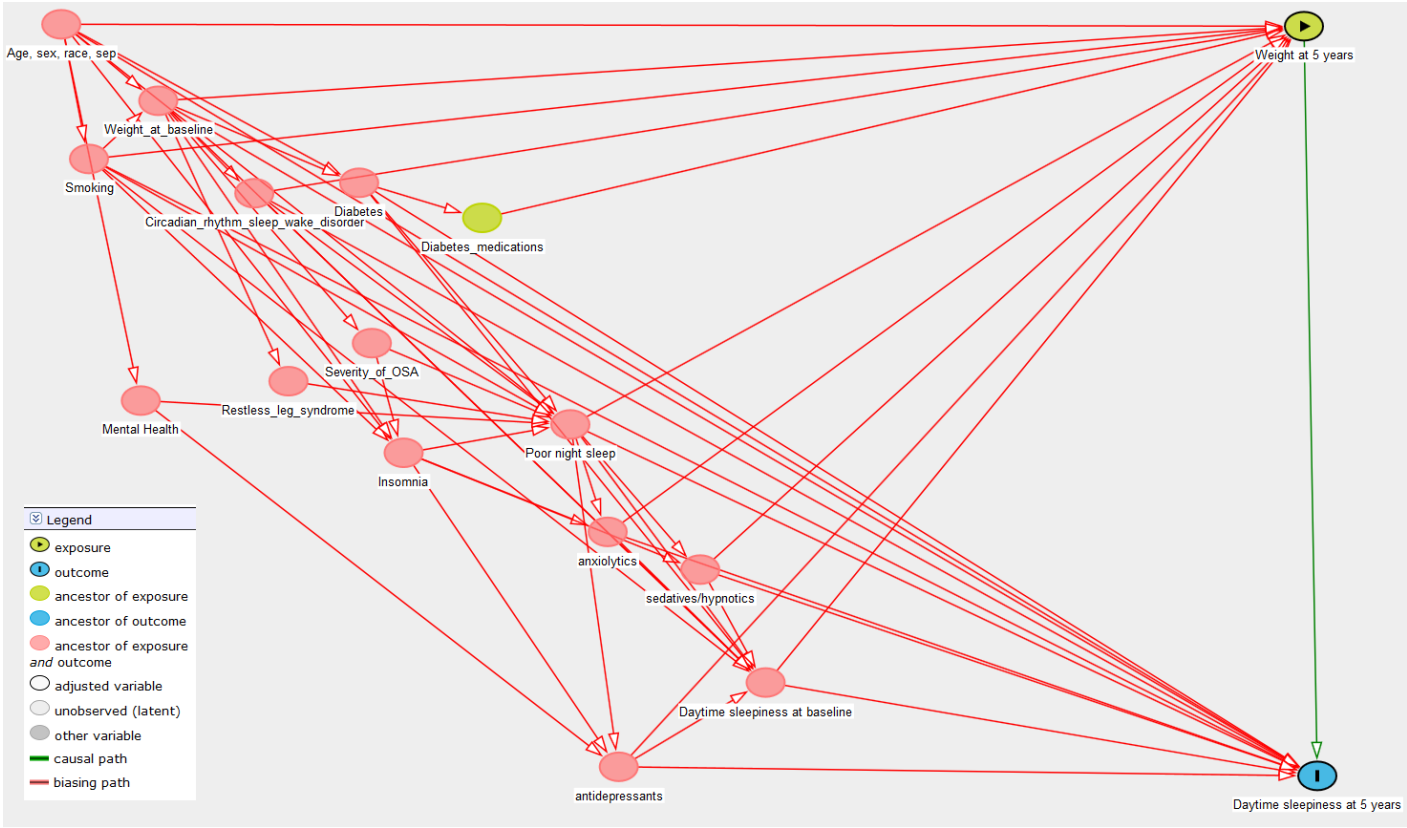

Fig. A.1 The Directed Acyclic Graph

According to our directed acyclic graph, which was built based on our prior knowledge and previous research publications in the field, the minimum sufficient adjustment set for estimating the total effect of weight change on daytime sleepiness are age, sex, race, socioeconomic position, circadian-rhythm sleep-wake disorders, baseline level of daytime sleepiness level, diabetes status, poor night sleep, smoking, baseline weight, as well use of antidepressants, anxiolytics and sedatives/hypnotics

Abbreviations: SEP, Socioeconomic position.

CHAPTER 5

Change in daytime sleepiness following weight loss interventions in overweight or obese individuals

"Our findings support a causal relationship between obesity and EDS, and the likely benefit of weight loss interventions on daytime sleepiness. We recommend screening for EDS in patients with obesity and consideration of weight loss in treating obesity-related EDS."

5.1. Summary

The causal interpretation to our finding of a relationship between weight change and daytime sleepiness in Chapter 4, is limited by the lack of a clear temporal direction. Weight loss interventions assessing daytime sleepiness as an outcome, provides an opportunity to assess causation. We therefore conducted a systematic review and meta-analysis assessing the effect of weight loss interventions on daytime sleepiness, and through a meta-regression, assess the potential dose-response relationship between the amount of weight loss and the magnitude of change in daytime sleepiness. Through this review, we found that daytime sleepiness improves following both surgical and non-surgical weight loss interventions; with no significant difference between the average effect sizes produced from controlled and uncontrolled studies. Further, we found that there is a non-linear dose-response relationship between the amount of weight loss and the degree of change in daytime sleepiness. Our findings from this review further support the causal relationship between obesity and excessive daytime sleepiness, and the recommendation of weight loss interventions as a treatment option for excessive daytime sleepiness.

5.2. Publication: Does intentional weight loss improve daytime sleepiness?: A systematic review and meta-analysis

5.2.1. Declaration

In the case of Chapter 5, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Drafting protocol, literature search, literature synthesis, data extraction, data matching, statistical analysis, integrity of the data and accuracy of the data analysis, critical interpretation of the data, drafting manuscript	80%

The following co-authors contributed to the work. If co-authors are students at Monash University, the extent of their contribution in percentage terms must be stated:

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
Christopher Stevenson	Drafting protocol, data extraction, statistical analysis, accuracy of data analysis, critical interpretation of data, draftin manuscript	N/A
Evelyn Wong	Drafting protocol, data extraction, critical interpretation of the data, drafting manuscript	5%
Stephanie Tanamas	Drafting protocol, data extraction, critical interpretation of the data, drafting manuscript	N/A
Tara Boelsen-Robinson	Drafting protocol, data extraction, critical interpretation of the data, drafting manuscript	5%
Jonathan Shaw	Drafting protocol, criticial interpretation of the data, drafting manuscript	N/A
Matthew Naughton	Drafting protocol, criticial interpretation of the data, drafting manuscript	N/A
John Dixon	Drafting protocol, criticial interpretation of the data, drafting manuscript	N/A
Anna Peeters	Drafting protocol, literature search, data extraction, data matching, statistical analysis, critical interpretation of the data, drafting manuscript	N/A

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the candidate's and co-authors' contributions to this work*.

Candidate's Signature			**Date** 17/03/2017
Main Supervisor's Signature			**Date** 17/03/2017

5.2.2. Manuscript

Does intentional weight-loss improve daytime sleepiness? – A systematic review and meta-analysis

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Obesity Treatment/Obesity Comorbidity

Does intentional weight loss improve daytime sleepiness? A systematic review and meta-analysis

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Summary

Obesity is associated with excessive daytime sleepiness, but its causality remains unclear. We aimed to assess the extent to which intentional weight loss affects daytime sleepiness. Electronic databases were searched through 24 October 2016. Studies involving overweight or obese adults, a weight loss intervention and repeated valid measures of daytime sleepiness were included in the review. Two independent reviewers extracted data on study characteristics, main outcome (change in daytime sleepiness score standardized by standard deviation of baseline sleepiness scores), potential mediators (e.g. amount of weight loss and change in apnoea–hypopnoea index) and other co-factors (e.g. baseline demographics). Forty-two studies were included in the review. Fifteen before-and-after studies on surgical weight loss interventions showed large improvements in daytime sleepiness, with a standardized effect size of −0.97 (95% confidence interval [CI] −1.21 to −0.72). Twenty-seven studies on non-surgical weight loss interventions showed small-to-moderate improvement in daytime sleepiness, with a standardized effect size of −0.40 (95%CI −0.52 to −0.27), with no difference between controlled and before-and-after studies. We found a nonlinear association between amount of weight loss and change in daytime sleepiness. This review suggests that weight loss interventions improve daytime sleepiness, with a clear dose–response relationship. This supports the previously hypothesized causal effect of obesity on daytime sleepiness. It is important to assess and manage daytime sleepiness in obese patients.

Keywords: Daytime sleepiness, intervention, obesity, weight loss.

Abbreviations: AHI, apnoea–hypopnoea index; BMI, body mass index; CPAP, continuous positive airway pressure; EDS, excessive daytime sleepiness; ESS, Epworth Sleepiness Scale; OSA, obstructive sleep apnoea; RCT, randomized controlled trial.

Introduction

Obesity is increasing worldwide (1) and has been associated with a wide range of poor health conditions (2), including excessive daytime sleepiness (EDS) (3,4). EDS, defined as the increased likelihood of falling asleep when one's intention is to remain awake (5), is associated with increased risk of motor accidents (6,7), occupational injuries (8), absenteeism (9) and decreased academic (10–12) and professional performance (13,14). EDS is a relatively common public

health problem. While causality is difficult to ascertain, weight loss interventions provide an opportunity to identify the direct effect of changes in weight on changes in daytime sleepiness.

A number of weight loss interventions have evaluated daytime sleepiness as a secondary outcome, but there has been little synthesis of these results. In 2013, Araghi *et al.* (15) synthesized the effect of weight loss interventions on obstructive sleep apnoea (OSA), exploring daytime sleepiness as a secondary outcome. They found that in randomized controlled trials (RCTs) of lifestyle interventions, daytime sleepiness did not improve despite improvements in severity of OSA. However, because daytime sleepiness was treated as a secondary outcome, this likely led to exclusion of studies that should otherwise be included into an analysis of daytime sleepiness. On the other hand, Iftikhar *et al.* (16) found significant overall improvement in daytime sleepiness following exercise interventions with or without weight loss.

Through a systematic review and meta-analysis, we aim to assess the effect of participation in weight loss interventions on daytime sleepiness in overweight and obese individuals and the role of the degree of weight loss in this effect. We also aim to explore the role of other potential mediators including change in severity of OSA and change in sleep duration.

Methods

The protocol to this systematic review and meta-analysis was registered in PROSPERO (registration number: CRD42014015477) (17).

Search strategies

Relevant articles were collected up to 24 October 2016 from Medline, CINAHL, EMBASE, SPORTDiscus and the Cochrane Library, using a set of search terms related to weight loss and daytime sleepiness (Table S1). Searches were limited to intervention studies, published in English. We also manually searched through reference lists of selected articles and reviews and scanned for related citations and bibliographies identified through PubMed and Google Scholar.

To test the robustness of our search strategy, we selected a few systematic review articles that assessed the effect of weight loss interventions on other non-sleep-related health outcomes and assessed their included studies for eligibility.

Eligibility criteria

- Type of studies: Controlled and uncontrolled studies were included. Uncontrolled studies were included to support results from controlled studies, which are small in number.
- Type of participants: Studies with adult participants (≥18 years old) and overweight and/or obese anthropometric measures at baseline were included.
- Types of interventions: Studies involving behavioural, surgical, pharmaceutical and any other type of weight loss interventions were included. Intervention arms involving a combination of weight loss with any other treatment affecting daytime sleepiness, such as continuous positive airway pressure (CPAP) therapy, were excluded.
- Type of comparison: Studies with control groups of placebo or no intervention were included. When the control group involved other forms of weight loss intervention, we regarded the individual treatment arms as independent before-and-after studies. If the control group included non-weight-loss intervention that affects daytime sleepiness, such as CPAP therapy, the control group was disregarded and the intervention group of the study was treated as a before-and-after study. If a placebo control was present, but there were more than one weight loss intervention groups of similar type, the intervention groups were combined and treated as one.
- Type of outcome measures: The preferred tool of measurement is the Epworth Sleepiness Scale (ESS). However, studies that included other commonly used objective sleepiness scores (such as the Multiple Sleep Latency Test and Maintenance of Wakefulness test) or subjective sleepiness scores from validated questionnaires (such as the Karolinska Sleepiness Scale, Stanford Sleepiness Scale, Visual Analogue Scale and the Sleep–Wake Activity Inventory) were also included in our review.
- Length of follow-up: For studies including multiple follow-up time points, only data from the earliest follow-up time point (immediate to the conclusion of the weight loss programme) were considered.
- Type of publication: Only peer-reviewed articles were included.

Study selection

The titles and abstracts of all identified citations were screened for inclusion by W. N. Full texts were reviewed by W. N. and one other independent reviewer (A. P., S. K. T., E. W., T. B. or C. S.) when eligibility for inclusion was not clear from the abstract. Disagreements were resolved through discussion. Authors were contacted for further clarification when needed.

Data extraction

From each intervention study, data on year of publication, year of study, country of origin, type of weight loss intervention, duration of intervention, type of study design

(controlled or uncontrolled), duration of study, study design details (including method of sampling, random allocation and blinding), sample size, response rate, dropout rate, pre-intervention and post-intervention details on main outcome (daytime sleepiness), pre-intervention and post-intervention details on potential mediators (e.g. anthropometric measures, sleep duration and severity of sleep apnoea) and potential baseline sources of heterogeneity (e.g. mean age, gender, education level and proportion of study participants receiving any other treatments affecting EDS) were extracted by W. L. N. and one other author (A. P., S. T., E. W., T. B. or C. S.). The two independent datasets were matched by W. L. N., and any discrepancies were resolved through discussion. Where necessary, authors were contacted and a second attempt at contact was made if replies were not received within a month.

Assessment for study quality

The quality of before-and-after studies was assessed using the guidelines developed by the Effective Public Health Practise Project (18). Each of the domains was rated as 'strong', 'moderate' or 'weak' according to the criteria provided. For controlled studies, we used the Cochrane risk-of-bias tools (19). Each of the domains was rated as 'low risk', 'high risk' or 'unclear risk' according to the criteria provided. We removed quality assessment for participant blinding as it is often not applicable in weight loss interventions and assessor blinding as a majority of the included studies used self-reported measures of daytime sleepiness.

Data synthesis

There are different ways of calculating effect sizes, with each method prone to biases in varying degrees (20). We selected the calculation for each study design with the least propensity for bias. In this meta-analysis, for uncontrolled studies, effect size was calculated as the mean change in sleepiness score divided by standard deviation of baseline sleepiness score. For controlled studies, we performed the same calculations, separately for intervention and control groups. The effect size from the control group was subtracted from the effect size of the intervention group, to give the overall effect size from controlled studies.

The calculation of standard error for the aforementioned effect sizes involved correlation coefficients between repeated measures of daytime sleepiness. When this was not reported or could not be calculated from available data, study authors were contacted. If we received no reply, we performed imputation using correlation coefficients from other included studies.

Full details of data synthesis can be found in the supporting information.

Data analysis

Effect sizes from different types of study designs (RCT vs. before-and-after study) and weight loss interventions (surgical vs. non-surgical) were pooled separately, using random-effects models to take into account between-studies variation. I^2 test statistics were used to determine the degree of heterogeneity between studies within each set of analyses, with $I^2 < 25\%$, $25\% \leq I^2 < 50\%$ and $50\% \leq I^2 < 75\%$ indicating low, medium and high levels of heterogeneity, respectively (21).

We subsequently performed a series of univariate meta-regression analyses (22) using data from before-and-after studies and intervention arms of RCTs, to assess potential sources of heterogeneity. The resulting adjusted R^2 describes the proportion of between-studies variance explained by the covariate being analysed. The covariates of interest included study design (type of sleepiness measurements, duration of study and duration of non-surgical intervention), baseline demographics (mean age, percentage male and percentage who completed tertiary education), baseline anthropometric measures (weight, body mass index [BMI] and waist and neck circumferences), baseline sleep health measures (apnoea–hypopnoea index [AHI] and sleep duration) and proportion receiving treatment affecting daytime sleepiness at baseline (percentage using CPAP and percentage on modafinil).

Change in anthropometric measures and change in sleep measures were also considered as potential sources of heterogeneity. These factors were additionally assessed as potential mediators of change in daytime sleepiness following weight loss interventions, similarly through univariate meta-regression analyses.

We used funnel plot and Egger's test to assess for potential publication bias.

All analyses were performed using STATA® version 12 (StataCorp, College Station, TX).

Results

Search results

The search resulted in 11,103 articles. We screened all titles and abstracts, reviewed 458 full-text articles and identified a total of 44 eligible studies for inclusion in the systematic review (Fig. 1).

Study characteristics

The characteristics of all 44 eligible studies are summarized in Table 1. Three studies (23–25) were excluded from quantitative analysis because of incomplete data reporting (even after contacting authors).

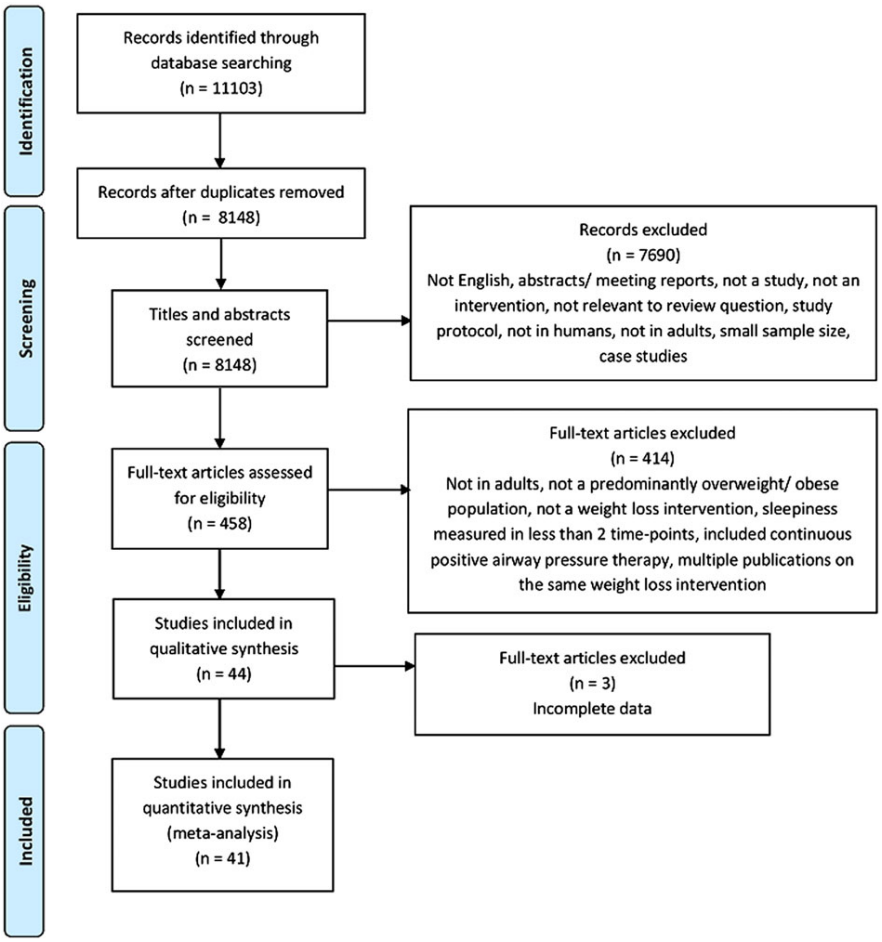

Figure 1 Flow diagram of the study selection process. [Colour figure can be viewed at wileyonlinelibrary.com]

The 41 studies included in this review comprised 15 surgical studies and 26 non-surgical studies (Table 1). Of the 15 surgical studies, 13 were before-and-after studies and two were RCTs. However, the work of Aguiar *et al.* (26) was treated as a before-and-after study because the results from the control group were not reported; that of Dixon *et al.* (34) was split into two before-and-after studies as it involved two weight loss intervention groups (one surgical and one non-surgical) with no placebo control group. Of the 26 non-surgical studies, 15 were RCTs and 11 were before-and-after studies. However, comparison groups from four of the RCTs (35,44,45,49) were excluded as they received CPAP therapy; the remaining intervention groups were treated as before-and-after studies. Morgan *et al.* (62) reported results on two groups of weight loss interventions of similar type, with a placebo control group. The two intervention groups were combined to form one intervention group; and the control group was retained. This resulted in 42 studies, 11 of which were RCTs and 31 (treated as) before-and-after studies, representing 2,284 participants with a mean age of 48.4 (range 37.9–68.0) and with 61.9% being male.

Most of the studies originated from Australia (n = 7) and the USA (n = 11); others were from Finland, Sweden, Mexico, the Netherlands, Canada, Italy, Japan, China, Brazil, Turkey, Spain, Kuwait, Egypt and France. A variety of weight loss interventions were described, including bariatric surgery (through gastric banding, sleeve gastrectomy, gastric bypass, gastroplasty and intragastric balloon), lifestyle modification (low-energy/very-low-energy diet, calorie-restricted and fat-restricted diet, counselling on exercise and diet, aerobic and resistance training and pedometer intervention) and drug trial (sibutramine, phentermine, topiramate, liraglutide, orlistat and zonisamide). A single intervention often combined more than one approach to aid/maintain weight loss. The median duration of intervention was 3 months; and the median study duration was 6 months. Sixty-four per cent of the studies were performed only in individuals with baseline OSA. All but three of the included studies used ESS to assess daytime sleepiness

Table 1 Study characteristics of eligible studies

Publication	*N**	Study duration (months)	Type of intervention†	Duration of intervention (months)	Mean/median age (years)	Male (%)	Baseline BMI (kg m^{-2})	Sleepiness tool	Baseline sleepiness score	Baseline CPAP use (%)	Baseline OSA (%)
Before-and-after studies											
Aguiar *et al.*, 2014 [26]‡	16	3	Surgical	NR	40.1	19	48.15 (SD 8.58)	ESS	6.92 (SD 6.54)	NA	87.5
Barnes *et al.*, 2009 [27]	12	4	Lifestyle	4	42.3§	25§	36.1 (SD 4.3)	ESS	8.7 (SD 5.1)	NA	NA
Borel *et al.*, 2012 [28]	47	12	Lifestyle	12	49.3§	100	30.6 (SD 3.1)§	ESS	9 (SD 5)§	NA	63.6
Busetto *et al.*, 2009 [29]	17	6	Surgical	6	NA	100	55.8 (SD 9.9)	ESS	11.2 (SD 5.2)	NA	100
Del Genio *et al.*, 2016 [30]	36	60	Surgical	NR	38	33.3	51.3 (SD 11.6)	ESS	16.75 (SD 2.45)	NA	100
Dilektasli *et al.*, 2016 [31]	52	6	Surgical	NR	**37.1**	**24**	Median 47 (range 39–67)	ESS	9.0 (SD 4.6)	0	NA
Dixon *et al.*, 2001 [32]	123	12	Surgical	NR	41§	20	46.0 (SD 7.5)	ESS	9.1 (SD 5.7)	8	33
Dixon *et al.*, 2005 [33]	25	17.7	Surgical	NR	44.7	72	52.7 (SD 9.5)	ESS	12.8 (SD 7.0)	92	100
Dixon *et al.*, 2012 [34],¶	30	24	Surgical	NR	47.4§	57§	46.3 (SD 6.0)	ESS	**13.17 (SD 5.71)**	NA	100
Dixon *et al.*, 2012 [34],¶	30	24	Lifestyle	1–1.5	50§	60§	43.8 (SD 4.9)	ESS	**12.33 (SD 6.66)**	NA	100
Ferland *et al.*, 2009 [35]‡	22	12	Drug and lifestyle	12	49	86	36.8 (SD 4.2)	ESS	13 (SD 5)	0	NA
Fujii *et al.*, 2010 [36]	10	4	Lifestyle	4	50.7	100	30.7 (SD 2.5)	ESS	9.1 (SD 4.0)	100	100
Fusco *et al.*, 2014 [23] (excluded)	57	24	Surgical	NR	44.7§	38.5	45.0§	ESS	NA	NA	100
Gilardini *et al.*, 2013 [37]	54	3	Lifestyle	3	56.6	0	37.6 (SD 4.1)**	ESS	5.8 (SD 4.2)	NA	100
Gomez-Peralta *et al.*, 2015 [38]	**86**	1	Drug	1	58.2§	49§	**38.7 (SD 6.7)**	ESS	6.3 (SD 4.6)	NA	NA
Haines *et al.*, 2007 [25] (excluded)	391	3	Surgical	NR	45§	17.5§	56 (SEM 1)	ESS	Median 44 (range 4–97)	82	82.8
Hakala *et al.*, 2000 [39]	13	1.5	Lifestyle	1.5	NA	NA	Median 35.0 (range 30.4–38.1)	VAS	100 mm	NA	100
Holty et al., 2011 [40]	142	6	Surgical	NR	43.7§	20.6§	44.8 (SD 7.9)§	ESS	7.9 (SD 4.5)§	NA	19.7

(*Continues*)

Table 1 (Continued)

Publication	*N**	Study duration (months)	Type of intervention†	Duration of intervention (months)	Mean/median age (years)	Male (%)	Baseline BMI (kg m^{-2})	Sleepiness tool	Baseline sleepiness score	Baseline CPAP use (%)	Baseline OSA (%)
Karakose *et al.*, 2014 ([41])	17	8.4	Surgical	NR	40.0	29.4	48.5 (SD 6.5)	ESS	8.35 (SD 5.57)	NA	100
Lettieri et al., 2009 ([42])	24	1.1	Surgical	NR	47.9	25	51.0 (SD 10.4)	ESS	15.0 (SD 4.9)	100	100
Lojander *et al.*, 1999 ([43])	23	1.5	Lifestyle	1.5	48	96	36 (SD 3)	VAS	47 mm (SD 30)	NA	NA
Masa *et al.*, 2015 ([44])‡	67	2	Lifestyle	2	60.0	44.0	44 (SD 7)	ESS	11 (SD 5.3)	NA	100
Masa et al., 2016 ([45])‡	46	2	Lifestyle	2	69	17	40 (SD 5.6)	ESS	8.5 (SD 4.2)	NA	NA
Nerfeldt *et al.*, 2008 ([46])	30	6	Lifestyle	2	52§	72.7§	40 (SD 5)	ESS	**8.9 (SD 4.3)**	NA	100
Norman *et al.*, 2000 ([47])	9	6	Lifestyle	6	48	89	31.2 (SD 4.6)	ESS	**14.6 (SD 4.4)**	55.6	100
Phillips *et al.*, 2009 ([48])	90	6	Lifestyle and drug	6	46.5	100	34.1 (SD 2.7)	ESS	13.3 (SD 3.7)	0%	100
Rasheid *et al.*, 2009 ([24]) (excluded)	98	6	Surgical	NR	46§	21§	54 (SEM 1)	ESS	12 (SEM 0.1)	58§	NA
Schutz *et al.*, 2013 ([49])‡	7	2	Lifestyle	2	42.28	100	28.14 (SD 1.63)	ESS	14.14 (SD 5.64)	NA	100
Shaarawy *et al.*, 2016 ([50])	22	12	Surgical	NR	37.2	59	48.2 (SD 7.3)	ESS	16.8 (SD 6.8)	NA	100
Suliman *et al.*, 2016 ([51])	20	60	Surgical	NR	31.25§	29.2§	60.51 (SD 8.97)	ESS	5.4 (SD 2.54)	75	100
Valencia-Flores *et al.*, 2009 ([52])	29	13.7	Surgical	NR	37.9	45	56.5 (SD 12.7)**	MSLT	**4.54 (SD 4.26)**	NA	NA
Varela *et al.*, 2007 ([53])	56	1	Surgical	NR	46	36	49 (SD 9)	ESS	13.7 (SD 5.5)	52	NA
Verhoef *et al.*, 2013 ([54])	98	2	Lifestyle	2	NA	26	**31.9 (SD 3.2)**	ESS	5.5 (SD 3.3)	NA	NA
Zou *et al.*, 2015 ([55])	44	9	Surgical	NR	48	41	31.1 (SD 3.4)	ESS	6.8 (SD 4.7)	NA	100%
						Controlled studies					
Blackman *et al.*, 2016 ([56])	345	8	Drug	8	48.5§	72§	38.9 (SD 6.4)§	ESS	Intervention: 9.2 (SD 5.1); control: 10.3 (SD 5.4)	0	Intervention: 100; control: 100
Desplan *et al.*, 2014 ([57])	22	1	Lifestyle	1	NA	NA	Intervention: 29.9 (SD 3.4); control: 31.3 (SD 2.5)	ESS (and OSLER)	Intervention: 13.6 (SD 4.5); control: 8 (SD 5.7)	Intervention: 0; control: 0	Intervention: 100; control: 100

(*Continues*)

Table 1 (Continued)

Publication	*N**	Study duration (months)	Type of intervention†	Duration of intervention (months)	Mean/median age (years)	Male (%)	Baseline BMI (kg m^{-2})	Sleepiness tool	Baseline sleepiness score	Baseline CPAP use (%)	Baseline OSA (%)
Eskandari *et al.*, 2014 ([58])	28	1	Drug	1	53.9	92.9	Intervention: 31 (SD 3); control: 31 (SD 2)	ESS	Intervention: 13 (SD 6); control: 12 (SD 4)	Intervention: 0?; control: 0?	Intervention: 100; control: 100
Johansson *et al.*, 2009 ([59])	63	2.25	Lifestyle	2.25	48.8	100	Intervention: 34.4 (SD 2.9); control: 34.8 (SD 2.9)	ESS	Intervention: 9 (SD 5); control: 7 (SD 5)	Intervention: 100; control: 100	Intervention: 100; control: 100
Kline *et al.*, 2012 ([60])	43	3	Lifestyle	3	47.0	56	NA	ESS (and PVT)	Intervention: 11.1 (SE 0.9); control: 7.3 (SE 0.9)	Intervention: 0; control: 0	100
Morgan *et al.*, 2012 ([61])	86	3.5	Lifestyle	3.5	44.4	100	Intervention: 30.7 (SD 3.6); control: 30.2 (SD 3.5)	ESS	Intervention: **6.3 (SD 4.5)**; control: **7.1 (SD 4.6)**	NA	NA
Morgan *et al.*, 2013 ([62])††	159	6	Lifestyle	3	49.7	100	Online: 32.8 (SD 3.4); resources: 32.4 (SD 3.3); control: 33.1 (SD 3.9)	ESS	Online: 6.8 (SD 3.8); resources: 5.9 (SD 3.8); control: 6.7 (SD 3.8)	NA	NA
Ng *et al.*, 2015 ([63])	104	4	Lifestyle	4	51.6	75	Intervention: 30.2 (SD 3.9); control: 30.5 (SD 4.2)	ESS	Intervention: 11.4 (SD 5.7); control: 10.2 (SD 4.7)	Intervention 37.7; control: 46.5	Intervention: 100; control: 100
Sengul *et al.*, 2009 ([64])	20	3	Lifestyle	3	51.2	100	Intervention: 29.79 (SD 2.66); control: 28.42 (SD 5.42)	ESS	Intervention: 8.20 (SD 6.14); control: 3.42 (SD 5.07)	NA	Intervention: 100; control: 100
Tuomilehto *et al.*, 2009 ([65])	72	12	Lifestyle	12	51.3	74	Intervention: 33.4 (SD 2.8); control: 31.4 (SD 2.7)	ESS	Intervention: 10.1 (SD 5.0); control: 9.9 (SD 4.8)	Intervention: 0%; control: 0%	Intervention: 100; control: 100
Winslow *et al.*, 2012 ([66])	45	7	Drug	7	52.4	53.3	Intervention: 36.0 (SD 3.07)**; control: 35.3 (SD 3.14)**	ESS	Intervention: 10.5 (SD 5.42)**; control: 9.8 (SD 4.3)**	Intervention: 0?; control: 0?	Intervention: 100; control: 100

Bolded data were obtained via communication with study authors.

*Total number of participants included in the final analysis of change in daytime sleepiness, after taking into account dropout or imputation.

†Description of the main type of weight loss approach used in the study. Studies may include other ancillary approaches to aid and/or maintain weight loss.

‡Originally a controlled study but treated as a before-and-after study.

¶Originally a controlled study but treated as two before-and-after studies.

§Imputed from pre-dropout data.

**Weighted average.

††Multiple weight loss intervention groups combined and treated as one.

BMI, body mass index; CPAP, continuous positive airway pressure; ESS, Epworth Sleepiness Scale; MSLT, Multiple Sleep Latency Test; NA, not available; NR, not relevant; OSA, obstructive sleep apnoea; OSLER, Oxford Sleep Resistance Test; PVT, Psychomotor Vigilance Test; SD, standard deviation; SEM; standard error of the mean; VAS, Visual Analogue Scale.

(Visual Analogue Scale, n = 2; Multiple Sleep Latency Test, n = 1); mean baseline ESS scores in these studies ranged from 5.3 to 16.8, with a mean (SD) of 10.1 (3.2). Mean baseline BMI was 39.9 (range 28.1–61.0) kg m^{-2}.

Intervention effect on daytime sleepiness

All of the surgical weight loss studies included in this meta-analysis were (treated as) before-and-after studies. The overall mean effect size for surgical weight loss interventions was −0.97 (−1.21 to −0.72), suggesting a moderate to large beneficial effect of surgical weight loss interventions on daytime sleepiness (roughly equivalent to a 4.8-point reduction in ESS scores) (Fig. 2). The overall mean effect size for non-surgical weight loss interventions was −0.40 (−0.52 to −0.27), suggesting a small to moderate beneficial effect of non-surgical weight loss interventions on daytime sleepiness (roughly equivalent to a 2.6-point reduction in ESS scores) (Fig. 3). When stratified by type of study design, mean effect size was −0.45 (95% confidence interval [CI] −0.60 to −0.29) from before-and-after studies and −0.28 (−0.48 to −0.08) from RCTs, the difference between which was not significant, 0.14 (95%CI −0.17 to 0.45). The level of heterogeneity was high in before-and-after studies, for both surgical (77.0%) and non-surgical interventions (66.9%); the level of heterogeneity was lower in RCTs of non-surgical interventions (29.7%).

Meta-regression: investigating baseline sources of heterogeneity

Table 2 shows that of all baseline characteristics considered, type of weight loss intervention contributed most to the heterogeneity of our included studies (39%). Variation in mean baseline weight also contributed to the heterogeneity at a similar level among those studies that reported mean baseline weight (n = 33). Variation in mean age, mean ESS score, mean BMI and prevalence of EDS (n = 18) also had substantial contribution (≥20%) to the between-studies heterogeneity in our meta-analysis. Variation in type of study design, mean baseline sleep duration, duration of study and mean baseline waist circumference explained less of the between-studies heterogeneity (≤10%).

Gender, mean baseline AHI and baseline prevalence of OSA did not explain any of the between-studies heterogeneity, which is consistent with the fact that most of the studies included in our meta-analysis were from predominantly male populations with baseline OSA.

Meta-regression: baseline study characteristics associated with greater improvement in daytime sleepiness

Results from univariate meta-regression analyses on baseline study characteristics suggest that surgical weight loss intervention, lower mean age, higher baseline weight/BMI

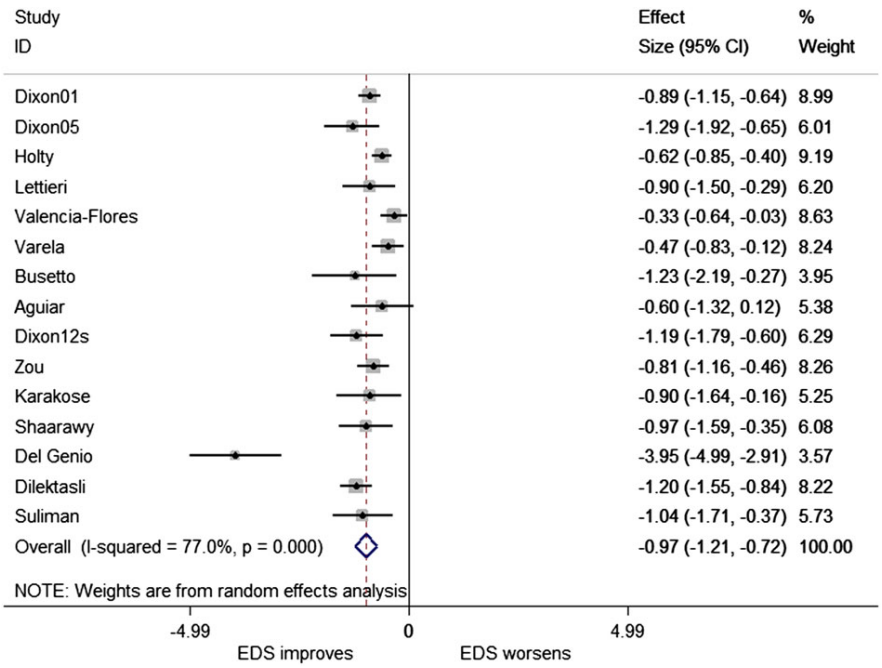

Figure 2 Forest plot of the effect sizes from surgical weight loss interventions. Note: All of the surgical studies were (treated as) before-and-after studies. CI, confidence interval; EDS, excessive daytime sleepiness. [Colour figure can be viewed at wileyonlinelibrary.com]

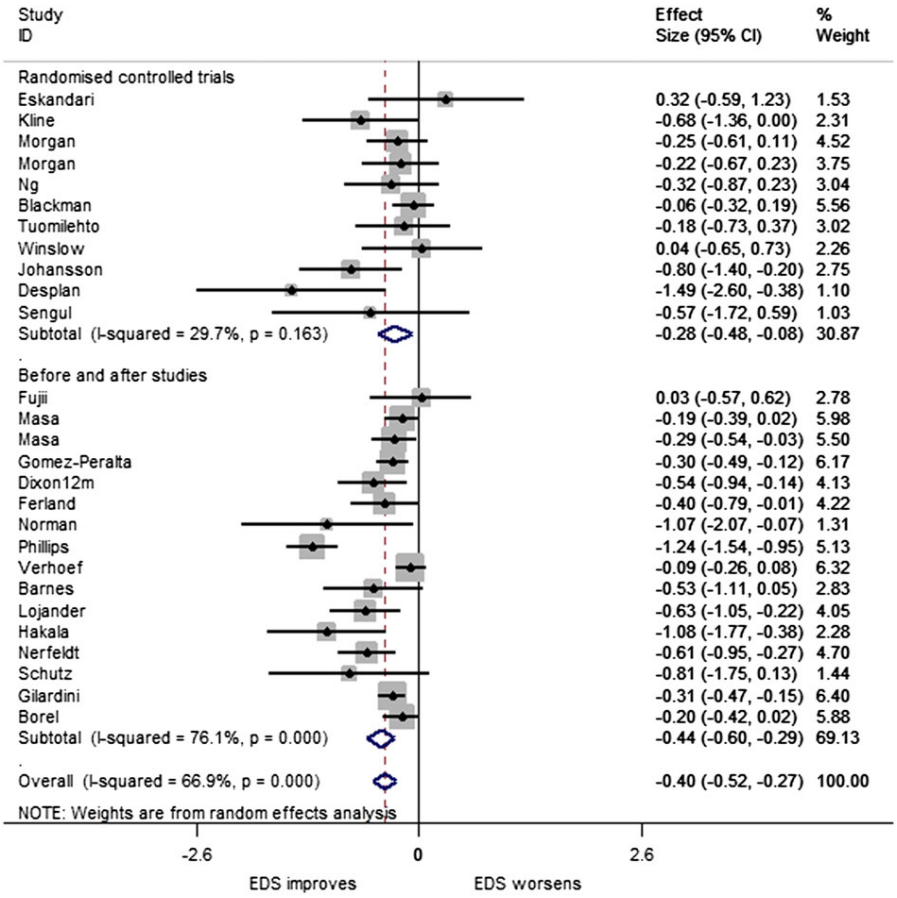

Figure 3 Forest plot of the effect sizes from non-surgical weight loss interventions, stratified by study designs. CI, confidence interval; EDS, excessive daytime sleepiness. [Colour figure can be viewed at wileyonlinelibrary.com]

and higher baseline ESS scores were associated with greater improvement in daytime sleepiness (Table 2).

Meta-regression: investigating a dose–response relationship

We found evidence for a nonlinear dose–response relationship between amount of weight loss and effect size (Table 3 and Fig. 4, n = 33). The relationship was L shaped; which means that daytime sleepiness improved with weight loss, but the rate of this improvement decreased with increasing magnitude of weight loss. A similar result was found in the analysis between amount of BMI reduction, amount of waist circumference reduction and effect size (Fig. S1).

There was no evidence for a dose–response relationship between effect size and AHI reduction (n = 27), change in neck circumference (n = 20) and change in sleep duration (n = 19).

Sensitivity analyses

The study quality for all included studies was assessed and presented in Tables 4a and 4b. Excluding before-and-after studies with more than one 'weak' rating (n = 1) and RCTs with more than one 'high risk' (n = 0) rating did not change the result of our meta-analysis and meta-regression. Excluding before-and-after studies with any 'weak' rating (n = 15) and RCTs with any 'high risk' rating (n = 1) did not alter results from meta-analysis of surgical weight loss interventions; but pooled effect sizes between RCTs and before-and-after studies of non-surgical weight loss interventions were more closely approximated (RCTs: −0.31, 95%CI −0.50 to −0.11; before-and-after: −0.35, 95%CI −0.47 to −0.23), and the overall effect size from surgical studies became slightly larger (−1.13, 95%CI −1.59 to −0.68).

Excluding the only study with measured, instead of self-reported, daytime sleepiness did not alter the results of our meta-analysis in a substantial manner. The results from our meta-regression analyses remained unchanged; except for the association between change in AHI and change in daytime sleepiness, which became significant. Excluding a study with a distinctively long follow-up (5 years) and great magnitude of effect size (Del Genio *et al.*) from the surgical meta-analysis produced a slightly smaller effect size (−0.82, 95%CI −0.99 to −0.66) but remained significant.

Table 2 Meta-regression univariate analysis: baseline factors associated with change in daytime sleepiness

Study characteristics	*n*	Coefficient (effect size)	95% confidence interval	Adjusted R^2 (%)*
Type of intervention				
Non-surgical	27	Ref	Ref	38.7
Surgical	15	−0.51	−0.81 to −0.21	
Type of study design				
Before-and-after studies	31	Ref	Ref	7.6
Randomized controlled trials	11	0.30	−0.06 to 0.65	
Duration of non-surgical interventions				
≤3 months	16	Ref	Ref	0.2
>3 months	11	−0.09	−0.36 to 0.18	
Duration of study				
≤6 months	27	Ref	Ref	3.90
>6 months	15	−0.26	−0.60 to −0.08	
Baseline demographics				
Mean age	35	0.03	0.01 to 0.06	27.1
Gender				
<75% Male	23	Ref	Ref	0.5
≥75% Male	14	0.20	−0.17 to 0.56	
Baseline anthropometric measures				
Mean baseline weight (kg m^{-2})	33	−0.01	−0.02 to −0.01	35.9
Mean baseline BMI (kg m^{-2})	42	−0.02	−0.04 to −0.01	22.6
Mean baseline waist circumference (cm)	24	−0.01	−0.02 to 0.00	4.8
Mean baseline neck circumference at (cm)	23	−0.06	−0.17 to 0.05	−0.8
Baseline sleep health measures				
Mean ESS at baseline (unit)	39	−0.08	−0.13 to −0.03	24.5
Mean AHI at baseline (events per hour)	29	−0.00	−0.01 to 0.01	−8.9
Mean sleep duration at baseline (h)	19	0.18	−0.05 to 0.40	9.8
%EDS at baseline	18	−0.01	−0.02 to 0.00	19.7
%OSA at baseline	31	−0.00	−0.01 to 0.01	−7.9
Treatment affecting daytime sleepiness				
%CPAP at baseline	20	−0.00	−0.01 to 0.00	−8.0

*Adjusted R^2 can have a negative value, which would mean that the covariate(s) explains less of the heterogeneity than would be expected by chance. AHI, apnoea–hypopnoea index; BMI, body mass index; CPAP, continuous positive airway pressure; ESS, Epworth Sleepiness Scale; EDS, excessive daytime sleepiness; OSA, obstructive sleep apnoea.

Imputation using different values of correlation coefficient did not change our results. Excluding studies with imputed correlation coefficient produced greater effect size from meta-analysis of non-surgical weight loss interventions (−0.49, 95%CI −0.70 to −0.29). For the latter, the difference between before-and-after studies and RCTs became larger (0.39, 95%CI 0.03 to 0.75) and significant.

Risk of bias

Publication/reporting bias was assessed through funnel plots and Egger's test. We detected potential risk of reporting bias against studies producing unfavourable effect on daytime sleepiness, through asymmetry of the funnel plots, which is more profound in the surgical (S2a) than non-surgical studies (S2b). We found evidence for bias through Egger's test in the surgical group (p = 0.02), but not in the non-surgical group (p = 0.06).

Discussion

This is the first systematic review and meta-analysis that has assessed the effect of weight loss interventions on daytime sleepiness as a primary outcome. Here, we demonstrated that daytime sleepiness consistently improved following surgical and non-surgical weight loss interventions. There was

Table 3 Meta-regression analysis: potential mediators of change in daytime sleepiness following weight loss interventions

Study-level covariates	*n*	Coefficient (effect size)	95% confidence interval	Adjusted R^2 (%)
Change in anthropometric measures				
Log of mean weight loss (kg)	33	−0.26	−0.39 to −0.13	59.3
Log of mean BMI reduction (kg m^{-2})	36	−0.23	−0.35 to −0.10	48.3
Log of mean waist circumference reduction (cm)	20	−0.19	−0.37 to −0.01	26.8
Mean neck circumference reduction (cm)	20	−0.09	−0.25 to 0.07	4.7
Change in sleep health measures				
Mean AHI reduction (events per hour)	27	−0.02	−0.03 to 0.00	24.8
Mean change in sleep duration (h)	19	−0.25	−1.10 to 0.59	−7.7

Abbreviations: BMI, body mass index; AHI, apnoea–hypopnoea index.

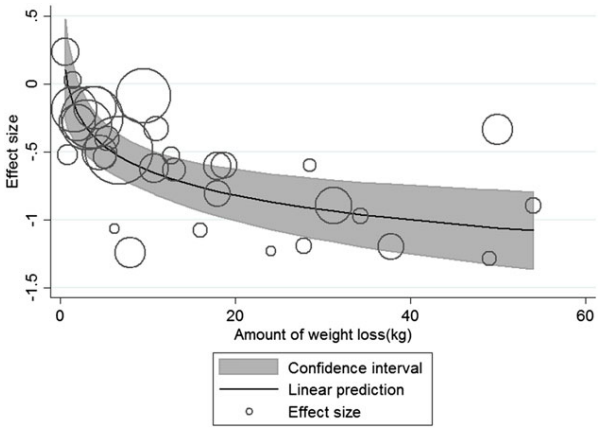

Figure 4 Meta-regression plot between effect size and amount of weight loss. Note: The area of each circle is inversely proportional to the variance of the effect size estimate. One outlier (Del Genio *et al.*) with an effect size of −3.95 is not shown in this figure.

no substantial effect size difference between RCTs and before-and-after studies. Further, there appears to be a nonlinear dose–response relationship between the amount of weight loss/BMI reduction and improvement in daytime sleepiness.

Contrary to our findings, Araghi *et al.* (15) found that in RCTs, daytime sleepiness did not improve following lifestyle weight loss interventions. This is likely to be due to differences in methodology. The primary outcome of their review was AHI, not daytime sleepiness, which means studies assessing daytime sleepiness but not AHI were excluded from the review. They also required all study participants to be diagnosed with OSA at baseline. These strict study selection criteria resulted in the inclusion of a very small number of studies (n = 3), reducing their statistical power. The pooled effect size from our review is also different from that of Araghi *et al.* (15). Their method of calculating effect sizes for RCTs assumed that random allocation at baseline was successful, in terms of daytime sleepiness. We have found that this is not true in some studies (64) and have chosen a method that allows for differences in the starting level of daytime sleepiness.

Our review has shown evidence for a dose–response relationship between weight loss/BMI reduction/waist circumference reduction and change in daytime sleepiness. This finding supports the previous hypothesis on the causal effect of obesity on EDS; but the pathways through which this occurs remained unclear. Current evidence suggests that obesity may cause EDS through a range of pathways, including OSA; overactivation of sympathetic nervous system; irregular hormonal, inflammatory and metabolic regulation; and other obesity-related chronic conditions that disturb night-time sleep, such as diabetes and depression (67). Future studies may consider exploring the causal pathways between obesity and EDS using individual-level data.

A wide range of weight loss interventions were included in this review. Our finding on a collective dose–response relationship between amount of weight loss and change in daytime sleepiness suggests the possibility that weight loss may benefit daytime sleepiness, independent of the methods through which weight loss was achieved (e.g. diet, physical activity or surgery). Future studies may assess whether the degree of improvement in daytime sleepiness varies with different types of weight loss. This cannot be assessed in the current review as a majority of the included studies involved more than one weight loss approach.

Another important and novel finding is the nonlinear association between amount of weight loss and change in daytime sleepiness. The rate of improvement in daytime sleepiness seems to attenuate with higher amount of weight loss. This phenomenon (floor effect) has been shown in individual weight loss studies, assessing other obesity-related health outcomes (68,69). This information needs to be taken into account when choosing between weight loss interventions. How much weight should obese individuals lose to obtain the greatest benefit with the minimum side effects?

We did not find evidence for a dose–response relationship between AHI reduction and improvement in daytime

Table 4a Quality assessment for before-and-after studies

Author, date of publication	Selection bias	Study design	Confounders	Data collection method	Withdrawal and dropouts
Aguiar *et al.*, 2014 ([26])*	Moderate	Moderate	Strong	Strong	Strong
Barnes *et al.*, 2009 ([27])	Weak	Moderate	Strong	Strong	Strong
Borel *et al.*, 2012 ([28])	Weak	Moderate	Strong	Strong	Strong
Busetto *et al.*, 2009 ([29])	Weak	Moderate	Strong	Strong	Strong
Del Genio *et al.*, 2016 ([30])	Moderate	Moderate	Strong	Strong	Strong
Dilektasli *et al.*, 2016 ([31])	Moderate	Moderate	Strong	Strong	Strong
Dixon *et al.*, 2001 ([32])	Moderate	Moderate	Strong	Strong	Weak
Dixon *et al.*, 2005 ([33])	Weak	Moderate	Strong	Strong	Weak
Dixon *et al.*, 2012† (surgical group) ([34])	Moderate	Moderate	Strong	Strong	Strong
Dixon *et al.*, 2012† (conventional therapy) ([34])	Moderate	Moderate	Strong	Strong	Strong
Ferland *et al.*, 2009 ([35])*	Moderate	Moderate	Strong	Strong	Strong
Fujii *et al.*, 2010 ([36])	Moderate	Moderate	Strong	Strong	Strong
Fusco *et al.*, 2014 ([23]) (excluded)	Moderate	Moderate	Strong	Strong	Weak
Gilardini *et al.*, 2013 ([37])	Moderate	Moderate	Strong	Strong	Strong
Gomez-Peralta *et al.*, 2015 ([38])	Weak	Moderate	Strong	Strong	Moderate
Haines *et al.*, 2007 (excluded) ([25])	Moderate	Moderate	Strong	Strong	Moderate
Hakala *et al.*, 2000 ([39])	Weak	Moderate	Strong	Strong	Strong
Holty *et al.*, 2011 ([40])	Moderate	Moderate	Strong	Strong	Weak
Karakose *et al.*, 2014 ([41])	Moderate	Moderate	Strong	Strong	Moderate
Lettieri *et al.*, 2009 ([42])	Moderate	Moderate	Strong	Strong	Strong
Lojander *et al.*, 1999 ([43])	Moderate	Moderate	Strong	Strong	Strong
Masa *et al.*, 2015 ([44])	Strong	Moderate	Strong	Strong	Strong
Masa *et al.*, 2016 ([45])*	Moderate	Moderate	Strong	Strong	Strong
Nerfeldt *et al.*, 2008 ([46])	Moderate	Moderate	Strong	Strong	Strong
Norman *et al.*, 2000 ([47])	Weak	Moderate	Strong	Strong	Strong
Phillips *et al.*, 2009 ([48])	Moderate	Moderate	Strong	Strong	Weak
Rasheid *et al.*, 2009 ([24]) (excluded)	Weak	Moderate	Strong	Strong	Strong
Schutz *et al.*, 2013 ([49])*	Moderate	Moderate	Strong	Strong	Weak
Shaarawy *et al.*, 2016 ([50])	Weak	Moderate	Strong	Strong	Strong
Suliman *et al.*, 2016 ([51])	Moderate	Moderate	Strong	Strong	Weak
Valencia-Flores *et al.*, 2009 ([52])	Weak	Moderate	Strong	Strong	Strong
Varela *et al.*, 2007 ([53])	Moderate	Moderate	Strong	Strong	Strong
Verhoef *et al.*, 2013 ([54])	Weak	Moderate	Strong	Strong	Strong
Zou *et al.*, 2015 ([55])	Moderate	Moderate	Strong	Strong	Strong

*Originally a controlled study but treated as a before-and-after study.
†Originally a controlled study but treated as two before-and-after studies.

Table 4b Quality assessment for randomized controlled trials

Author, date of publication	Random sequence generation	Allocation concealment	Incomplete outcome data	Selective reporting	Other sources of bias
Blackman *et al.*, 2016 ([56])	Unclear risk	Low risk	Low risk	Low risk	Low risk
Desplan *et al.*, 2009 ([57])	Unclear risk	Unclear risk	Low risk	Low risk	Low risk
Eskandari *et al.*, 2014 ([58])	Low risk	Unclear risk	High risk	Low risk	Low risk
Johansson *et al.*, 2009 ([59])	Low risk	Low risk	Low risk	Low risk	Low risk
Kline *et al.*, 2012 ([60])	Low risk	Low risk	Low risk	Low risk	Low risk
Morgan *et al.*, 2012 ([61])	Low risk	Unclear risk	Low risk	Low risk	Low risk
Morgan *et al.*, 2013 ([62])*	Low risk	Low risk	Low risk	Low risk	Low risk
Ng *et al.*, 2015 ([63])	Low risk	Unclear risk	Low risk	Low risk	Low risk
Sengul *et al.*, 2009 ([64])	Low risk	Unclear risk	Unclear risk	Unclear risk	Low risk
Tuomilehto *et al.*, 2009 ([65])	Low risk	Low risk	Low risk	Unclear risk	Low risk
Winslow *et al.*, 2012 ([66])	Low risk	Unclear risk	Low risk	Unclear risk	Low risk

*Multiple weight loss intervention groups combined and treated as one.

sleepiness. This is consistent with findings from previous epidemiological studies, which showed poor correlation between AHI and daytime sleepiness (3,67,70,71). This could be due to lack of association between OSA and EDS, but recent consensus postulated that this could also be due to AHI being a poor measure of OSA (72). The hypothesis of OSA as a mediator between obesity and EDS can be reassessed using other measures of OSA or when better measure for severity of OSA is developed.

Limitations

One limitation to our review is that in the meta-regression, we used effect sizes from before-and-after studies and the intervention arm of RCTs. In doing so, our effect sizes are prone to confounding factors and regression to the mean. However, we have shown that pooled effect sizes from RCTs and before-and-after studies of non-surgical weight loss interventions do not differ significantly.

Another limitation is the possibility of publication bias among surgical studies, as shown through funnel plot and Egger's test. Daytime sleepiness is often assessed as a secondary outcome, posing risk of selective reporting. However, the results of meta-analysis from surgical weight loss interventions appear consistent with that from non-surgical weight loss interventions, which have a more symmetrical funnel plot. This suggests that even if there is publication bias in surgical weight loss interventions, it is likely that only the magnitude of the pooled effect size would be affected, but not the overall conclusion of surgical weight loss interventions reducing daytime sleepiness. In sensitivity analysis of the higher-quality studies, similar results were seen, and these had little apparent publication bias.

An insufficient number of included studies reported change in categorical EDS. Therefore, we cannot conclude on the rate of clinically significant change in EDS following weight loss in our review.

Strengths

We conducted a comprehensive systematic search through multiple databases, minimizing the risk of excluding relevant studies. All types of weight loss interventions were included in this review, which allows comprehensive meta-regression analysis on the dose–response relationship between the amount of weight loss and change in daytime sleepiness. Completeness of the data was enhanced by a number of responses to queries for study authors. RCTs of weight loss interventions with non-placebo control arms were treated as uncontrolled studies, maximizing the utility of our limited study data.

Implications

This review concludes, for the first time, that surgical and non-surgical weight loss interventions in those who are overweight or obese are likely to benefit daytime sleepiness. From the perspective of obesity researchers and clinicians, this adds to the motivation of conducting weight loss interventions. From the perspective of sleep researchers and clinicians, this provides evidence that weight loss intervention could play a role in managing EDS in patients with obesity.

This review also provides evidence supporting a causal relationship between obesity and EDS through its findings of a dose–response relationship between change in weight/BMI and change in daytime sleepiness. Given possible consequences of daytime sleepiness such as motor vehicle accidents (6,7) and loss of productivity (13,14), it is crucial to include EDS in obesity management strategies; and clinicians should be advised to screen for EDS in patients with obesity.

Our review offers a deeper understanding on the relationship between obesity and sleep, an area that has been less explored relative to other obesity-related health outcomes. A full understanding of the consequences of obesity and the likely benefits of weight loss is central to the development of effective obesity management strategies and in estimating the burden of obesity.

Conclusion

Our findings support a causal relationship between obesity and EDS, and the likely benefit of weight loss interventions on daytime sleepiness. We recommend screening for EDS in patients with obesity and consideration of weight loss in treating obesity-related EDS.

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W. N. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the analysis.

Conflict of interest statement

A. P. reports grants from the National Health and Medical Research Council, others from Novo Nordisk, outside the submitted work. J. D. reports personal fees from the National Health and Medical Research Council, during the conduct of the study; personal fees from Apollo Endoscopy; personal fees from Bariatric Advantage; personal fees from Novo Nordisk; personal fees from iNova Pharmaceuticals; personal fees from Novartis; personal fees from Nestle; and personal fees from mdBriefcase, outside the submitted work. All other authors have nothing to disclose.

Supporting information

Additional Supporting Information may be found in the online version of this article, http://dx.doi.org/10.1111/obr.12498

Table S1. Ovid Medline search strategy
Figure S1. Meta-regression plot between effect size and amount of body mass index reduction
Figure S2. Funnel plot for (A) surgical and (B) non-surgical weight loss interventions
Supplementary text on data synthesis

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Supplementary Appendix

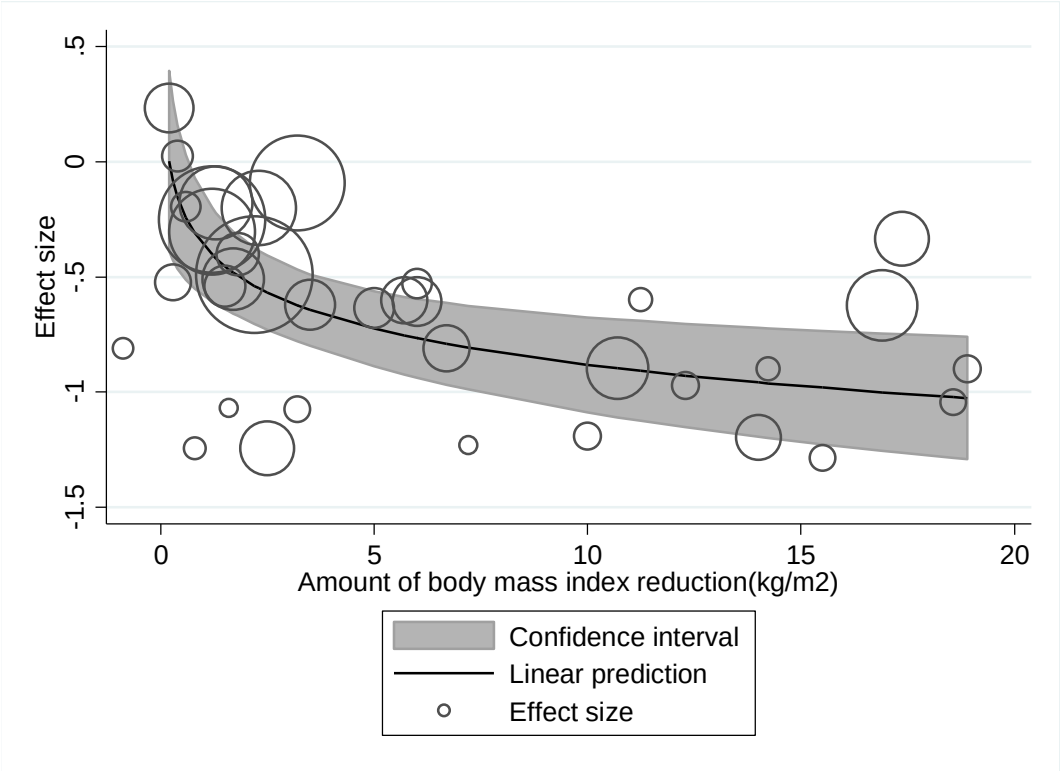
Does intentional weight loss improve daytime sleepiness? A systematic review and meta-analysis

W. L. NG, C. E. Stevenson, E. Wong, S. Tanamas, T. Boelsen-Robinson, J. E. Shaw, M. T. Naughton, J. D. Dixon, and A. Peeters

List of Contents

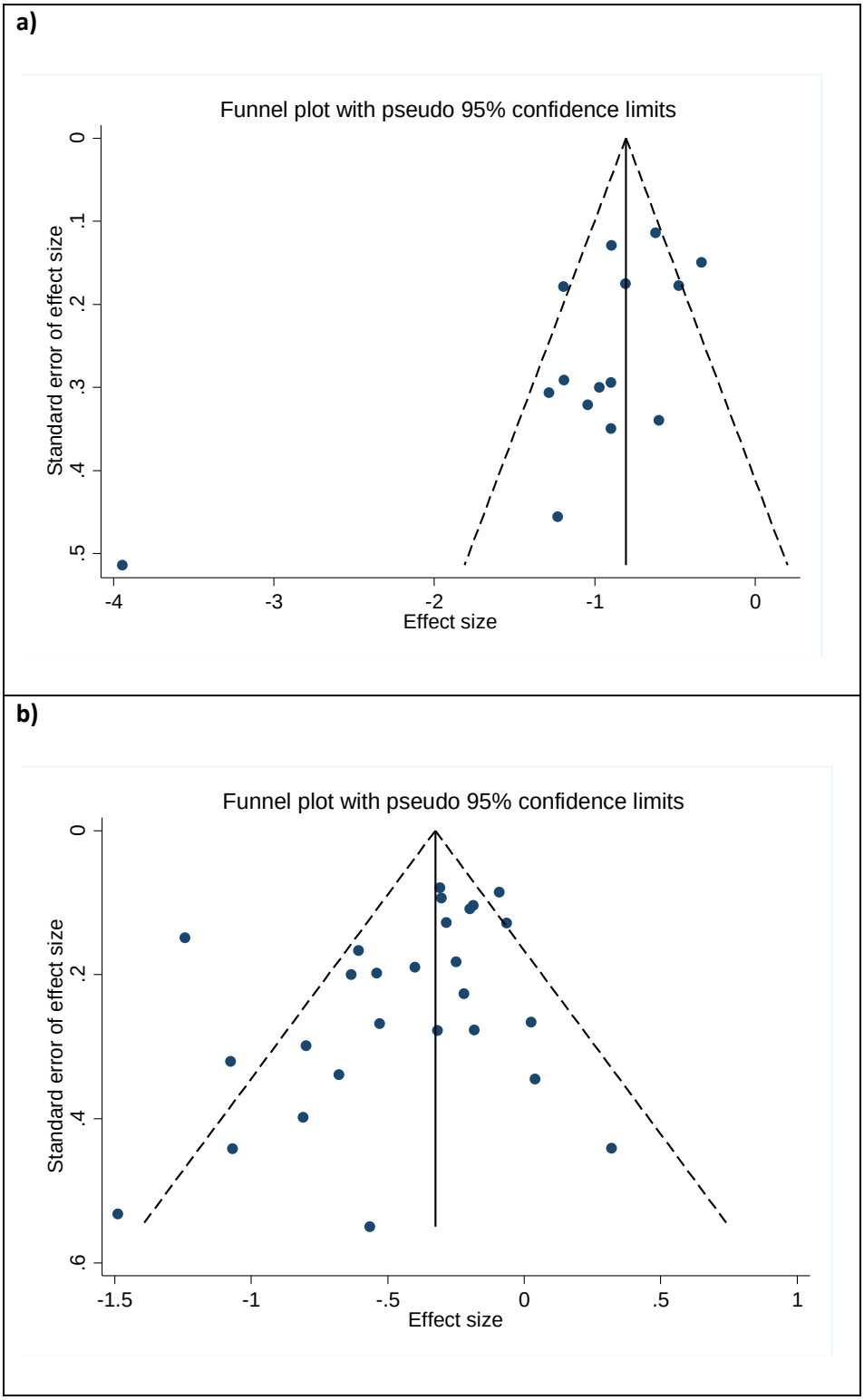
Supplementary Table S1. Ovid Medline search strategy

#	Searches
1	Weight Loss/ or weight reduction programs/
2	(weight* adj2 (loss* or change* or declin* or reduc* or decreas* or
3	Obesity/ or Obesity, Morbid/ or Obesity, Abdominal/ or exp
4	(Obesity or overweight).tw.
5	Anthropometry/
6	anthropometr*.tw.
7	exp Bariatrics/
8	(Bariatric* or (stomach adjl stapling) or (surg* adjl metabolic) or (gastr* adj2 bypass*) or gastrojejunostom* or gastroplast* or (bypass* adjl intestinal) or (jejuno* adj2 bypass*) or (ileo* adj2 bypass*) or
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10	exp "Disorders of Excessive Somnolence"' or exp Sleep Apnea
11	(sleepiness or sleepy or somnolen* or hypersomnolen* or drows* or
12	(sleep adj2 (apnea* or apnoea* or hypopnea* or hypopnoea* or
13	10 or 11 or 12
14	intervention studies/ or evaluation studies/ or exp clinical trial/ or exp clinical trials as topic/ or multicenter study/ or exp cohort studies/
15	(Intervention adj (study or studies)).tw.
16	(random* or trial* or placebo).tw.
17	(controlled clinical trial or Randomized Controlled Trial or Clinical
18	evaluation stud*.tw.
19	evaluation stud*.pt.
20	((follow-up or followup or longitudinal or cohort or prospective or retrospective) adj (study or studies)).tw.
21	14 or 15 or 16 or 17 or 18 or 19 or 20
22	9 and 13 and 21



Supplementary Figure S1. Meta regression plot between effect size and amount of body mass index reduction

Note: The area of each circle is inversely proportional to the variance of the effect size estimate. One outlier (Del Genio et al.) with effect size -3.95 is not shown in this figure.



Supplementary Figure S2. Funnel plot for a) surgical and b) non-surgical weight loss interventions

Supplementary text: Data synthesis

There are a few different ways to calculate effect size for continuous outcomes. The choice depends on the type of study design (controlled vs. uncontrolled study) and the question being asked (magnitude vs. significance). Morris et al[20] provides a comprehensive review of the different methods available and the type of bias each method is prone to. As described below, we selected the most appropriate method for the available study designs, with the least source of bias.

In this meta-analysis, for uncontrolled studies, effect size (ES) was calculated as mean change in sleepiness score divided by standard deviation of baseline sleepiness score. The standard error (SE) of this effect size was calculated using the following formula: [20,65]

$$ES = \frac{\bar{x}_{post} - \bar{x}_{pre}}{SD_{pre}}$$

$$SE = \sqrt{\frac{2(1-r)}{n} + \frac{ES^2}{2(n-1)}}$$

where $\bar{x}_{post}$ is the mean score of daytime sleepiness post-intervention, $\bar{x}_{pre}$ is the mean score of daytime sleepiness at baseline, $SD_{baseline}$ is the baseline standard deviation of mean sleepiness score, r is the correlation coefficient between daytime sleepiness scores at baseline and post-intervention, and n is the total sample size in the study.

For meta-analysis of controlled studies, effect size was calculated using the same formula as above, separately for intervention and control group. The effect size from control group was subtracted from the effect size of intervention group, to give the overall effect size from controlled studies. This formula is shown below, together with its standard error.

$$ES = ES_T - ES_C = \frac{\bar{x}_{post_T} - \bar{x}_{pre_T}}{SD_{pre_T}} - \frac{\bar{x}_{post_C} - \bar{x}_{pre_C}}{SD_{pre_C}}$$

$$SE = \sqrt{\frac{2(1-r_T)}{n_T} + \frac{{ES_T}^2}{2(n_T-1)}} + \sqrt{\frac{2(1-r_C)}{n_C} + \frac{{ES_C}^2}{2(n_C-1)}}$$

where $\bar{x}_{post}$ is the mean score of daytime sleepiness post-intervention, $\bar{x}_{pre}$ is the mean score of daytime sleepiness at baseline, $SD_{baseline}$ is the baseline standard deviation of mean sleepiness score, r is the correlation coefficient between daytime sleepiness scores at baseline and post-intervention, and n is the total sample size. The subscript 'T' refers to treatment or intervention group; and the subscript 'C' refers to the control group.

The correlation coefficient 'r' is often not reported. However, when standard deviation of baseline, post-intervention and change in daytime sleepiness scores are reported, it can be calculated using the following formula:[66]

$$r = \frac{SD_{pre}^2 + SD_{post}^2 - SD_{change}^2}{2SD_{pre}SD_{post}}$$

where SD_{pre} and SD_{post} are the standard deviations of mean daytime sleepiness score at baseline and post-intervention respectively; and SD_{change} is the standard deviation of change in daytime sleepiness score before and after the intervention.

When any component(s) in the above formula was not available (usually SD_{change}) the authors of the corresponding publication were contacted for further information. If we received no reply, we would impute 'r' from other studies. From studies that reported 'r' and those that provided enough information to allow

back-calculation of ‘r’, median ‘r’ was calculated separately for surgical and non-surgical studies, for intervention and control group, and for different measurement tool of daytime sleepiness. None of the two non-surgical studies that used visual analogue scale, reported ‘r’;[45,49] hence the ‘r’ for these studies were imputed using median ‘r’ from non-surgical studies that used Epworth sleepiness scale to assess daytime sleepiness.

We performed sensitivity analysis to assess how our results would differ if we had performed imputation using different values of correlation coefficient (first and third quartiles of the available ‘r’).

CHAPTER 6

Change in daytime sleepiness following a workplace physical activity intervention

"In this evaluation of participants in a 4-month pedometer workplace health program, we found no change in daytime sleepiness in general, but a sustained improvement for those with excessive daytime sleepiness at baseline. Around one-half of those with excessive daytime sleepiness at baseline no longer had EDS immediately upon conclusion of the program."

6.1. Summary

Through the systematic review in Chapter 5, we observed that physical activity interventions tend to produce minimum or no improvement in daytime sleepiness. This can be due to the small amount of weight loss that the physical activity interventions produced, or simply due to lack of power. In this Chapter, using readily available data, we assessed the change in daytime sleepiness following a four-month, pedometer-based, workplace physical activity program, in a cohort of the general working population in Melbourne, Australia. Our study results suggest that there may be both immediate and sustained improvement in daytime sleepiness, among those with excessive daytime sleepiness at baseline, after participation in the workplace physical activity program. The degree of improvement in daytime sleepiness was associated with the amount of reduction in body mass index. This finding confirms our previous findings on the relationship between obesity and excesive daytime sleepiness; and suggests a potential unforeseen benefit of a workplace physical activity program on daytime sleepiness. Future study may confirm our findings by including a control group.

6.2. Publication: The immediate and sustained long-term change in daytime sleepiness after participation in a workplace pedometer program: a prospective cohort study

6.2.1. Declaration

In the case of Chapter 6, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Study design, literature synthesis, statistical analysis, integrity of the data and accuracy of the data analysis, critical interpretation of the data, drafting manuscript	70

Note that 60% of the work was from my B.MedSci(Hons) thesis

The following co-authors contributed to the work. If co-authors are students at Monash University, the extent of their contribution in percentage terms must be stated:

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
Rosanne Freak-Poli	Study design, literature synthesis, critical interpretation of the data, drafting manuscript	N/A
Chris Stevenson	Statistical analysis, critical interpretation of the data, drafting manuscript	N/A
Anna Peeters	Study design, literature synthesis, statistical analysis, critical interpretation of the data, drafting manuscript	

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the candidate's and co-authors' contributions to this work*.

Candidate's Signature	[redacted]	**Date** 17/03/2017
Main Supervisor's Signature	[redacted]	**Date** 17/03/2017

6.2.2. Manuscript

The immediate and sustained long-term change in daytime sleepiness after participation in a workplace pedometer program: a prospective cohort study

Ng W.L., Freak-Poli R., Stevenson C., Peeters A.

J Occup Environ Med. 2015;57(8):873-81.

ORIGINAL ARTICLE

The Immediate and Sustained long-Term Changes in Daytime Sleepiness After Participation in a Workplace Pedometer Program

A Prospective Cohort Study

Winda Liviya Ng, BMedSc (Hons), Rosanne Freak-Poli, BSc, BHealthSc, PhD, Christopher Stevenson, BSc (Hons), MSc, PhD, and Anna Peeters, BSc(Hons), PhD

Objective: To assess the potential benefit of a workplace physical activity program on daytime sleepiness. **Methods:** A total of 685 participants of a 4-month workplace physical activity program were assessed for daytime sleepiness (Epworth Sleepiness Scale [ESS]) at baseline, 4 months (postprogram), and 12 months. Changes in ESS were analyzed using multilevel mixed linear regression. **Results:** In the total population, no changes in ESS scores were observed; 0 to 4 months: −0.2 (95% CI: −0.5 to 0.0), 4 to 12 months: 0.1 (95% CI: −0.2 to 0.4). In participants with baseline excessive daytime sleepiness (ESS > 10, $n = 109$), ESS scores improved significantly by −2.2 (95% CI: −3.0 to −1.4) at 4 months, sustained at 12 months; and almost half no longer had excessive daytime sleepiness by end of program. **Conclusions:** This study suggests that for employees with excessive daytime sleepiness, short- and long-term improvement in daytime sleepiness may be an unforeseen benefit of workplace physical activity programs.

In past decades, workplace physical activity levels have decreased across the globe and sedentary time has increased.[1] This is concerning because people commonly spend a significant proportion of their time at work and low physical activity as well as high sedentary time have been associated with adverse health effects.[2,3] For these reasons, there has been increasing implementation of workplace physical activity programs.[4–7] We and others have shown the effectiveness of a workplace physical activity program in improving several health factors, such as waist circumference and blood pressure.[8–11] Nevertheless, the benefits of such programs are likely to be much broader than prevention of cardiometabolic diseases.

From the Obesity and Population Health Unit (Ms NG, Drs Freak-Poli and Peeters, and Mr Stevenson), Baker IDI Heart and Diabetes Institute; Department of Epidemiology & Preventive Medicine, Faculty of Medicine, Nursing & Health Sciences, School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria, Australia; Department of Epidemiology (Dr Freak-Poli), Erasmus Medical Centre, Rotterdam, The Netherlands; and School of Health & Social Development (Dr Stevenson), Faculty of Health, Deakin University, Melbourne, Victoria, Australia.

This study was supported in part by the Victorian Government's OIS Program and funded by the Australian Research Council and the Foundation of Chronic Disease Prevention in the workplace, which is associated with the Global Corporate Challenge. The study design, analysis, and interpretation of data, the writing of the manuscript, and the decision to submit the manuscript for publication were solely at the discretion of the Monash researchers, independent of Global Corporate Challenge or The Foundation's involvement. W.N.G. is supported by a Monash Graduate Scholarship, a Monash International Postgraduate Research Scholarship and a Baker IDI Bright Sparks Top-Up Scholarship. R.F.P. is supported by an NHMRC ECR Fellowship (1053666). C.S. is funded by an ARC Discovery Project Grant. A.P. is funded by an NHMRC Career Development Award.

The authors declare no conflicts of interest.

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One potential benefit of physical activity programs is the reduction of excessive daytime sleepiness (EDS), which is the increased propensity of falling asleep when one's intention is to remain awake.[12] This hypothesis is based on the known beneficial effect of physical activity on the quality of night-time sleep[13] and inflammatory profiles associated with obesity or obstructive sleep apnea,[14] both of which are important drivers of EDS. In addition, we and others have recently shown that EDS shares a range of risk factors with noncommunicable diseases (NCDs), such as older age, high body mass index (BMI), poor dietary behavior, and poor mental health.[15,16] Consequently, workplace healthy lifestyle programs targeting obesity and NCDs may exert concurrent benefit on EDS. Such workplace health programs may also act on daytime sleepiness due to other characteristics such as increasing social networking and motivation at work.

Greater daytime sleepiness is associated with a range of negative impacts in our everyday life, especially in a workplace setting. This includes increased risk of motor accidents,[17] occupational injuries,[17–19] reduced professional performance,[20] and increased absenteeism.[21] Nevertheless, workplace healthy lifestyle evaluations rarely assess daytime sleepiness as an outcome. Morgan et al[10] conducted a randomized controlled trial of a workplace weight-loss program in overweight male shiftworkers and observed an insignificant trend toward improvement in daytime sleepiness at the end of the program. This could be due to lack of power or true lack of change. To the best of our knowledge, no other study has assessed the impact of workplace physical activity programs on daytime sleepiness.

This study aimed to assess the potential short- (4 months, end of program) and sustained long-term (12 months, 8 months postprogram completion) effect of a workplace physical activity program on daytime sleepiness. We used data from 762 voluntary participants of the Global Corporate Challenge® Evaluation Study, a longitudinal study on the health effects of a 4-month, 10,000 steps pedometer program for Australian (Melbourne) workers. We hypothesized that participation in the Global Corporate Challenge workplace pedometer program would result in improvements in daytime sleepiness.

METHODS

The Global Corporate Challenge Program

The Global Corporate Challenge (GCC) program is an annual, global, workplace physical activity program that encourages workers from across the globe to complete at least 10,000 steps per day, for 125 days, monitored using a pedometer.[22]

The GCC Evaluation Study

The GCC Evaluation Study recruited 762 eligible participants enrolled in the 2008 GCC program and assessed various health factors and conditions at baseline (start of program), 4 months (end of program), and 12 months (8 months postprogram completion) in Melbourne, Australia.[4,8]

From 16 April to 30 May 2008, Melbourne workplaces participating in the GCC program, and subsequently their respective employees, were contacted for voluntary involvement in the GCC Evaluation Study. The recruited study participants were (1) 18 years old or older, (2) able and willing to provide informed consent, and (3) employed at a participating workplace. Written consent was obtained from workplaces and individual participants who volunteered to participate in the study. More details on the methodology can be found in previous publications.[4,8]

Study Population

From the 762 eligible study participants, participants who were pregnant at baseline ($n = 4$), 4 months ($n = 9$), or 12 months ($n = 15$) were excluded from the analyses (Fig. 1). All participants with complete baseline Epworth Sleepiness Scale (ESS) assessment were included in the main analysis ($n = 685$).

Measurements

The ESS is a self-administered questionnaire that assesses the level of daytime sleepiness through eight commonly encountered daily activities, each rated from 0 to 3. A higher overall score represents a worse level of daytime sleepiness. The EDS is defined as total ESS score of more than 10.[12,23] The ESS has been validated against objective tools such as Multiple Sleep Latency test[23] and was also found to have a relatively high level of internal consistency and test–retest reliability.[24]

Selected cofactors were included in this study as potential predictors of change in daytime sleepiness (Table 1). Self-reported questionnaires were used to collect demographic, dietary pattern, and behavioral and psychosocial measures. The anthropometric measurements of height, weight, and hip and waist circumference were performed by trained staff using a 200-cm stadiometer, a 150-kg bathroom scale, and a Figure Finder tape measure, allowing measurements to the nearest 0.1 cm, 0.1 kg, and 0.1 cm, respectively.

Analysis

All analyses were performed using STATA® version 12.1.

To assess for potential selection bias, an attrition analysis of baseline cofactors was undertaken, comparing participants who completed follow-up surveys ($n = 406$) with those who did not attend or complete follow-up surveys ($n = 279$). Comparison was performed using regression to allow adjustment for workplace clustering effects.

In the primary analysis, changes in ESS scores were assessed continuously and categorically. Continuously, the ESS scores of the overall population at baseline, 4 months, and 12 months, were analyzed using multilevel mixed-effects linear regression. This method of analysis was chosen to take into account correlations between repeated measurements within an individual over time and to allow adjustment for workplace clustering effect. The multilevel linear mixed model also offers the advantage of utilizing information from incomplete data pairs, thereby minimizing loss of study power due to missing data. For this analysis, all participants who completed baseline ESS assessment ($n = 685$) were included. The same analysis was repeated, with stratification according to baseline EDS status (population with EDS at baseline, $n = 109$; population without EDS at baseline, $n = 576$), to identify any influence EDS might have on the association between participation in the program and change in the level of daytime sleepiness. Categorically, the proportion of those with EDS in the overall population at baseline, 4 months, and 12 months were analyzed using multilevel mixed-effects logistic regression. This method is analogous to the multilevel mixed-effects linear regression used in the continuous analysis of ESS.

To mitigate the limitation of not having a control group, a Regression to The Mean (RTM) analysis was conducted alongside

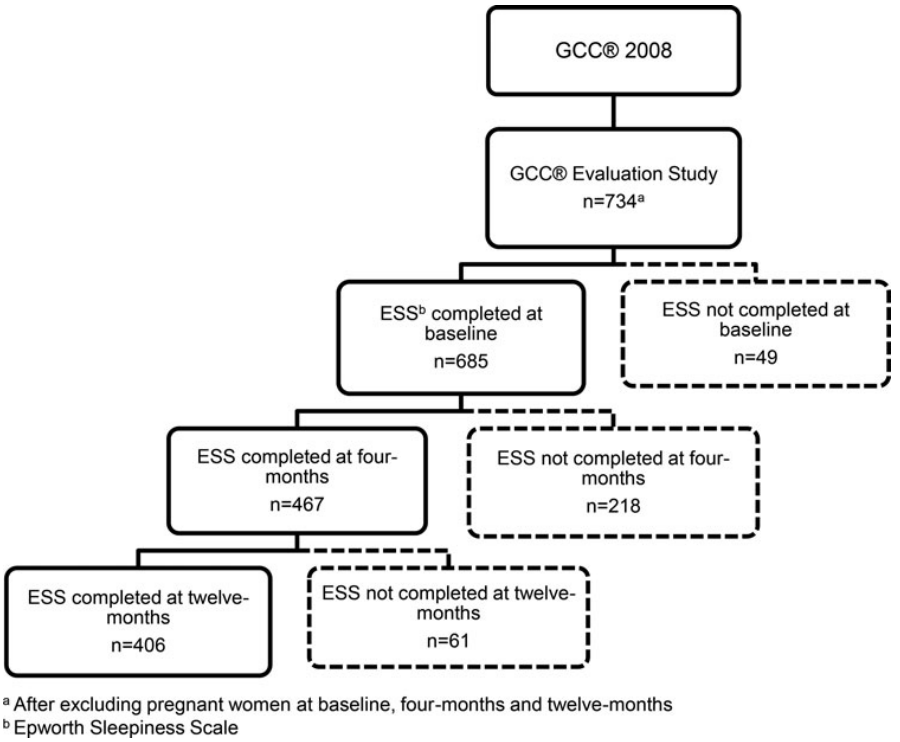

FIGURE 1. Recruitment and retainment overview.

TABLE 1. Potential Predictors of Change in Daytime Sleepiness

Variable	Description
Demographics	
Age and sex	
Education[25]	Dichotomized into nontertiary vs tertiary education
Occupation[26]	Categorized into four groups: "Manager," "Professional," "Associate professional," and "Clerical or service"
Dietary measures	
Fruit intake[27]	Adequate fruit intake defined as equal to or more than two servings per day
Vegetable intake[27]	Adequate vegetable intake defined as equal to or more than five servings per day
Takeaway food[28]	Categorized into three groups: "Once or less per month," "About once a week," and "More than once a week"
Behavioral measures	
Physical activity[25,29]	Using the World Health Organization's algorithm, the self-reported amount of time spent doing moderate- and/or vigorous-intensity physical activity in a typical week was used to estimate the Metabolic Equivalent hours (MET-hours), which is an equivalent of caloric expenditure of 1 kcal/kg/hr. MET-hours was assessed as a continuous variable. • Vigorous activity (METhours) = total number of hr/week × 8 MET • Moderate activity (METhours) = total number of hr/week × 4 MET
Sedentary time[25,29]	Assessed continuously in hr/day for a typical day (WHO STEP-wise Approach)
Anthropometric measures	
Body mass index	Derived from height and weight $\left(\text{BMI} = \frac{\text{weight (kg)}}{\text{height}^2(\text{m}^2)}\right)$, each measured by trained staff
Waist circumference	Measured by trained staff
General health and well-being	
Well-being	World Health Organization–5 well-being index,[30] scale: 0–25. Higher score reflects greater well-being
Psychological distress	Kessler-10 Psychological Distress Scale, scale: 10–50.[31] Higher score reflects worse level of psychological distress
Mental functioning	Short Form-12 (SF-12) questionnaire, scale: 0–100. [32] Higher score reflects better mental functioning
Physical functioning	SF-12 questionnaire, scale: 0–100. [32] Higher score reflects better physical functioning
Process measures	
Step count	The average daily number of steps taken by the study participant during the 4-month program

the stratified analysis for changes in continuous ESS. The RTM refers to a phenomenon where higher values tend to become lower and lower values, higher, after repeated measurements in a period of time, due to random variation. Using the RTM prediction model from Linden,[33] we estimated the potential contribution of RTM to the observed effects of the program on daytime sleepiness in study participants who did and did not have EDS at baseline. For this analysis, participants who completed baseline ESS assessment ($n = 685$) were included. Subsequently, we also used the Jacobson–Truax reliable change index (RCI)[34] to estimate individuals in whom apparent changes in ESS score were likely to be true changes, similarly on the basis of estimates of random variation. From this analysis, each individual study participant could be classified as (1) recovered: move from EDS to non-EDS category, (2) improved: decreased ESS scores without change in EDS category, (3) unclassifiable: unreliable change, (4) worsened: increased ESS scores without change in EDS category, or (5) deteriorated: move from non-EDS to EDS category, depending on their change in ESS between baseline and 4 months ($n = 467$), and between baseline to 12 months ($n = 495$). The unclassifiable category includes study participants who experienced changes that, according to the Jacobson–Truax RCI,[34] were statistically unreliable and likely due to measurement error and random variation.

In a secondary analysis, we analyzed potential predictors of change in daytime sleepiness at 4 and 12 months through regression analysis of 4- or 12-month ESS adjusting for baseline ESS in both the total population and the population with baseline EDS. This analysis was restricted to participants with complete ESS assessment at all three time-points (total population, $n = 406$; population with baseline EDS, $n = 68$). In the first model, only baseline nonvarying covariates were included as predictors of ESS scores at 4 and 12 months. In the second model, 4- and 12-month changes in selected covariates were included as predictors of ESS scores at 4 and 12 months respectively, with adjustment for baseline demographics. Physical activity was included as one of the predictors due to its hypothesized positive effect on daytime sleepiness. Other predictors were chosen on the basis of their previously identified association with ESS[15] or their indication of successful participation in the program (average step count). All cofactors were tested for correlation. Body mass index and psychological distress were included in the main model as they were more strongly correlated to ESS than their close counterparts, waist circumference (with BMI), well-being, and SF-12 mental functioning (with psychological distress). Cofactors not included in the main model were each analyzed in a separate multivariate model. This analysis was performed using multiple linear regression, with adjustment for workplace clustering effect.

Ethics

This study was conducted in accordance with Monash University Human Research Ethics approval, specifically by the Standing Committee on Ethics in Research involving Humans; Low impact Research Project Involving Humans (Authorization number: CF08/0271-2008000125).

RESULTS

Attrition Analysis

Participants who completed ESS at all three time-points were more likely to be older and more sedentary at baseline but achieved a higher step count during the program than those with incomplete ESS assessment at any of the three time-points (Table 2).

Change in ESS After Participation in the GCC Program

There was no change in the overall mean ESS scores at 4 months (end of program) or 12 months (follow-up) (Table 3). After stratification according to baseline EDS status, an improvement in ESS scores was observed in the baseline EDS group at 4 months, which was sustained at 12 months. No changes were observed in the non-EDS group at 4 or 12 months.

There was no change in the proportions of the overall population with EDS at 4 months and 12 months (Table 3). Stratification according to baseline EDS status showed that, in the baseline EDS group, the proportion with EDS decreased (from 100%) by 46.0% at 4 months, followed by a 1.3% increase at 12 months. In the non-EDS group, the proportion with EDS increased (from 0%) slightly to 7.4% at 4 months and 9.3% at 12 months. The extent to which the observed changes are likely to be independent of random variation was assessed using the Jacobson–Truax RCI later.

Regression to the Mean

The estimated change in ESS predicted by the RTM effect was −1.6 at 4 months, followed by a further −0.3 at 12 months in study participants with baseline EDS. This is a lesser change than the observed −2.4 at 4 and 12 months (Fig. 2). In contrast, the estimated RTM effect in study participants without EDS at baseline was smaller than the observed changes.

The Jacobson–Truax Reliable Change Index

At 4 months, in study participants with baseline EDS, 22.4% experienced significant recovery (moved from EDS to non-EDS category); 1.3%, improvement (decreased ESS scores without change in EDS category); 2.6%, worsening (increased ESS scores without

TABLE 2. Comparison of Baseline Characteristics Between Participants With Complete and Incomplete Epworth Sleepiness Scale Measures Across the Three Time-Points

	Completed ESS at All Three Time-Points ($n = 406$)	Incomplete ESS at Any of the Three Time-Points ($n = 279$)	*P*
ESS scores, unit	6.5 ± 4.1	6.6 ± 4.0	0.9
EDS, %	16.8	14.8	0.3
Demographics			
Age	41.6 ± 10.1	38.8 ± 10.7	<0.05
Sex (male, %)	43.6	37.8	0.3
Tertiary education, %	80.5	77.9	0.5
Occupation, %			
Manager	19.4	26.6	0.8
Professional	47.2	38.2	
Associate professional	20.2	15.8	
Clerical or service	13.1	19.3	
Dietary measures			
Fruit intake (meeting guidelines, %)	33.3	27.3	0.1
Vegetable intake (meeting guidelines, %)	16.5	12.0	0.1
Takeaway food, %			
Once or less per month	46.8	43.5	0.1
About once a week	40.9	41.0	
More than once a week	12.3	15.5	
Behavioral measures			
Physical activity, MET hr	38.9 ± 40.5	38.9 ± 51.4	1.0
Sedentary time, hr/d	8.4 ± 3.2	7.8 ± 3.5	<0.05
Anthropometric measures			
Body mass index, kg/m^2	26.9 ± 4.8	26.7 ± 4.7	0.7
Waist circumference, cm	88.7 ± 12.5	87.3 ± 12.5	0.3
Psychosocial measures			
Well-being, unit	15.0 ± 4.8	15.0 ± 4.9	0.9
Psychological distress, unit	17.8 ± 5.7	17.9 ± 6.0	0.7
SF-12, unit			
Mental functioning	49.4 ± 9.9	49.6 ± 9.9	0.8
Physical functioning	51.0 ± 7.4	49.7 ± 7.1	0.06
Process measures			
Step count, steps/d	11,839 ± 3,769	11,112 ± 3,636	<0.05

EDS, Excessive Daytime Sleepiness; ESS, Epworth Sleepiness Scale; SF-12, Short form-12.

TABLE 3. Change in the Epworth Sleepiness Scale at 4 Months (End of Program) and 12 Months (Follow-Up)

				Baseline to 4 Months		Four Months to 12 Months	
	Baseline	Four Months	Twelve Months	Mean Change	Difference (95% CI)	Mean Change	Difference (95% CI)
Overall sample; $n = 685$							
ESS (mean ± SD)	6.6 ± 4.1	6.3 ± 4.0	6.4 ± 4.1	−0.2	(−0.5 to 0.0)	0.1	(−0.2 to 0.4)
EDS, %	15.9	15.0	17.1	−0.9	OR = 0.9 (0.3 to 2.8)	2.1	OR = 1.3 (0.4 to 3.8)
Baseline nonexcessive daytime sleepiness group (ESS ≤ 10), $n = 576$							
ESS (mean ± SD)	5.3±2.8	5.4±3.3	5.5±3.5	0.1	(−0.1 to 0.4)	0.1	(−0.1 to 0.4)
EDS, %	0	7.4	9.3	7.4	NA	1.9	NA
Baseline excessive daytime sleepiness group (ESS > 10), $n = 109$							
ESS (mean ± SD)	13.3 ± 2.7	10.9 ± 3.9	10.9 ± 3.9	−2.2	(−3.0 to −1.4)*	−0.2	(−1.0 to 0.7)
EDS, %	100	54.0	55.3	−46.0	NA	1.3	NA

*$P < 0.05$.
EDS, Excessive Daytime Sleepiness; ESS, Epworth Sleepiness Scale; NA, not applicable.

change in EDS category) and 73.7%, unclassifiable (changes in ESS scores likely to be due to random variation). This suggests that of all the recoveries we observed in the baseline EDS group (ie, −46.0%; Table 3), at least half was likely to be independent of random variation. In study participants without EDS at baseline, there was a 2.8% rate of deterioration (moved from non-EDS to EDS group), 2.6% rate of worsening, 2.3% rate of improvement, and 92.3% unclassifiable change. This suggests that of all the deteriorations we observed in baseline non-EDS group (ie, 7.4%; Table 3), around one-third was likely to be independent of random variation.

Similar observations were made to 12 months.

Factors Associated With change in ESS at 4 Months and 12 Months After Participation in the GCC Program

Regression analysis was conducted in both the total population (data not shown) and study participants with baseline EDS. Here we report in detail, on the population of most interest, that with baseline EDS. In the sample with baseline EDS, further missing data ($n = 12$) for predictors analyzed at 4 and 12 months resulted in a final sample size of 56. Results from the model that includes only baseline nonvarying covariates showed that lower ESS scores at 4 months were associated with lower baseline ESS scores. No other baseline

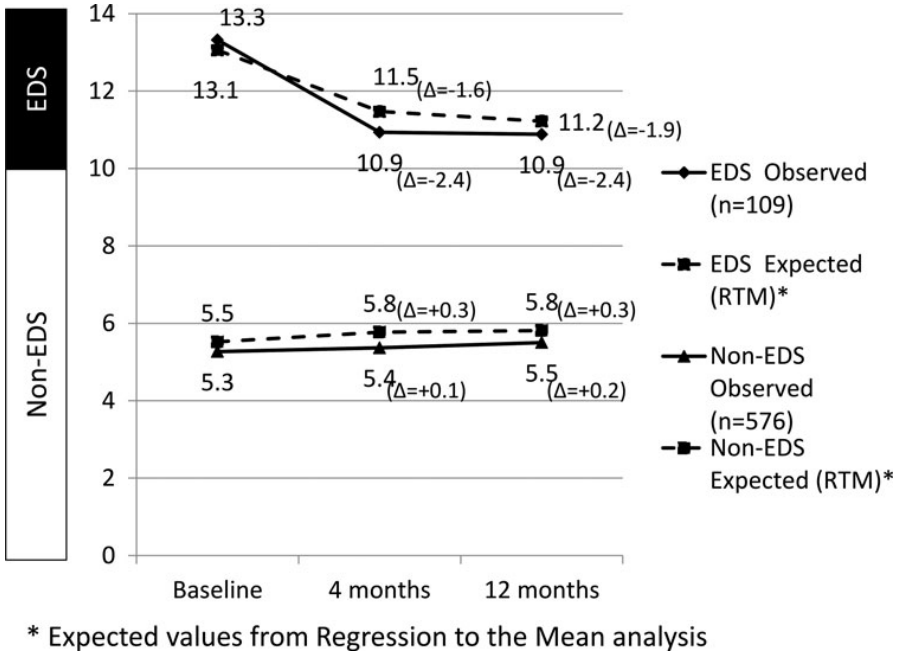

FIGURE 2. Comparison of the observed and expected Epworth Sleepiness Scale (ESS) scores at 4 and 12 months by baseline Excessive Daytime Sleepiness (EDS) status after estimation of the regression to the mean effect.

TABLE 4. Factors Associated With Change in Epworth Sleepiness Scale Scores at 4 Months and 12 Months in Study Participants With Baseline Excessive Daytime Sleepiness ($n = 56$)

	ESS at 4 Months, Coefficient (95% CI)	ESS at 12 Months, Coefficient (95% CI)
Baseline factors associated with change in ESS at 4 and 12 months		
ESS at baseline	0.83 (0.33 to 1.33)*	0.42 (0.05 to 0.78)*
Age (quadratic)		
Years	−0.31 (−0.79 to 0.17)	−0.17 (−0.87 to 0.53)
Years^2	0.00 (−0.00 to 0.01)	0.00 (−0.01 to 0.01)
Sex (female)	0.46 (−3.0 to 3.88)	0.37 (−1.11 to 1.87)
Tertiary education (completed)	−0.34 (−1.63 to 2.32)	−0.47 (−3.02 to 2.08)
Changes in covariates associated with change in ESS at 4 and 12 months[a]		
Dietary measures		
Fruit intake		
No change	Reference	
Improved	−2.99 (−5.11 to −0.87)*	0.26 (−3.46 to 3.98)
Worsened	−0.76 (−2.89 to 1.36)	−0.94 (−3.24 to 1.36)
Vegetable Intake		
No change	Reference	
Improved	−1.06 (−3.72 to 1.60)	−1.79 (−8.06 to 4.48)
Worsened	−1.09 (−3.10 to 0.91)	−0.58 (−4.82 to 3.67)
Takeaway food		
No change	Reference	
Improved	−0.43 (−2.99 to 2.13)	−0.07 (−1.37 to 1.52)
Worsened	0.38 (−1.13 to 1.89)	1.45 (−2.49 to 5.38)
Behavioral measures		
Physical activity, MET hr	0.01 (−0.01 to 0.03)	0.02 (−0.01 to 0.05)
Sedentary time, hr/d	−0.23 (−0.35 to −0.10)*	0.04 (−0.12 to 0.21)
Anthropometric measures		
Body mass index, kg/m^2[b]	0.79 (0.18 to 1.39)*	−0.00 (−0.38 to 0.38)
Waist circumference, cm[b]	0.03 (−0.17 to 0.22)	−0.07 (−0.20 to 0.06)
Psychosocial measures		
Psychological Distress, unit[c]	0.30 (0.10 to 0.50)*	0.14 (0.03 to 0.26)*
Well-being[c]	−0.07 (−0.23 to 0.09)	−0.10 (−0.20 to 0.01)
SF-12, unit		
Mental functioning[c]	−0.05 (−0.20 to 0.11)	−0.05 (−0.11 to 0.02)
Physical functioning	−0.16 (−0.30 to −0.01)*	0.04 (−0.16 to 0.24)
Process measures		
Step count (1000 steps/day)	−0.04 (−0.27 to 0.18)	0.17 (−0.14 to 0.49)

*$P < 0.05$.

[a]Adjusted for baseline demographics and baseline ESS scores.

[b]Because of the strong correlation between body mass index and waist circumference, each was analyzed in a different multivariate model, in such a way that they were not mutually adjusted. Body mass index was chosen to be in the main model.

[c]Because of the strong correlation between well-being, psychological distress, and mental functioning (SF-12), each was analyzed in a different multivariate model, in such a way that they were not mutually adjusted. Psychological distress was chosen to be in the main model.

EDS, Excessive Daytime Sleepiness; ESS, Epworth Sleepiness Scale; SF-12, Short form-12.

factors were associated with ESS scores at 4 or 12 months (Table 4). Results from the model that includes 4- and 12-month changes in selected covariates showed that increased fruit intake, increased sedentary time, decreased BMI, improved psychological distress, and increased physical functioning between baseline and 4 months were associated with lower (improved) ESS scores at 4 months. Of these, only improved psychological distress between baseline and 12 months continued to predict lower (improved) ESS scores at 12 months (Table 4). Change in physical activity was not associated with change in ESS scores; this was also true when it was mutually adjusted with average step count. Similar results were observed when participants with missing data were included (data not shown).

Similar findings were observed from analysis of the overall population

DISCUSSION

This study, evaluating changes in daytime sleepiness after participation in a workplace physical activity program, demonstrated that although overall there was no change in ESS, study participants with baseline EDS experienced significant improvement in ESS immediately after the program ended, and this improvement was sustained 8 months later. Furthermore, one-half of the study participants with baseline EDS experienced resolution upon conclusion of the program. We also found that a range of improvements

in lifestyle and health factors might be associated with improved daytime sleepiness at 4 and/or 12 months.

To our knowledge, this is the first study to assess the effect of a workplace pedometer program on daytime sleepiness in a mixed population of workers. Our results were similar to those of Morgan et al,[10] who reported a not-significant improvement in ESS in obese shiftworkers after a weight-loss program. The authors noted that the study might have been underpowered. A post hoc power calculation using the effect size from Morgan et al showed that this study has sufficient power (greater than 90%) to detect similar or greater change in ESS scores and we did not find a significant change in the overall study population. In this study, significant improvement was only found in study participants with baseline EDS. This gives rise to the hypothesis that it is important to assess improvement in daytime sleepiness in people with high baseline ESS scores or those in the EDS category.

Without limiting comparisons to workplace studies, other previous studies have also shown potential benefits of exercise on daytime sleepiness in those with a relatively high level of daytime sleepiness,[35–39] as well as in those with induced sleepiness through sleep-deprivation trials.[40–42] There are a few likely pathways for this effect. Daytime sleepiness is greatly influenced by nocturnal sleep and exercise is a recommended nonpharmacological approach to improve nocturnal sleep, through its BMI-lowering, muscle-strengthening, antianxiety, antidepressant, thermogenic and circadian phase-shifting effects.[13] It has been hypothesized that exercise may also improve daytime sleepiness by improving inflammatory profiles in people with obesity and/or obstructive sleep apnea,[14] one of the most common causes of EDS. Healthy lifestyle programs such as a workplace physical activity program may also exert mood-lifting effects on its participants through improved social life, improved motivation, and competitive environment, which in turn may improve their level of daytime sleepiness, as EDS has been closely associated with poor mental health in previous studies.[16,43] We have found preliminary evidence in support of this as improvements in the mental health markers were strongly associated with improvements in ESS scores.

In addition to an immediate improvement in ESS in those with baseline EDS at the end of the program, we also found that this beneficial change was sustained in the long term (8-month postprogram completion). To the best of our knowledge, none of the previous physical activity studies assessed potential sustained long-term effects on daytime sleepiness. We have shown that for employees with EDS, immediate and sustained long-term improvement in ESS could be a potential unforeseen benefit from workplace physical activity programs targeting obesity and NCDs.

In subsequent analyses, we explored whether any baseline or changes in cofactors were associated with improved ESS scores. The results suggested that increased sedentary time, increased fruit intake, decreased BMI, and physical functioning might be associated with lower ESS scores at 4 months, and an improvement in psychological distress was associated with lower (better) ESS scores at both 4 and 12 months. Our findings are concurrent with cross-sectional studies that hypothesized that improvement in diet, BMI, physical functioning, and mental health could be associated with improved ESS scores.[15,16,44] The observed relationship between sedentary time and ESS scores is counterintuitive. Nevertheless, a recent validation study of the Global Physical Activity Questionnaire, the tool we used to assess both physical activity and sedentary behavior, suggests that it correlates poorly with an accelerometer and is not recommended as a measure for change in sedentary behavior.[45] This could have affected our results. The lack of association between increased physical activity and improved ESS was not expected, but because of the small sample size of the baseline EDS sample, we cannot conclude whether it was a true lack of association or due to lack of power. This also applies to other not-significant predictors in the analysis. A larger sample size is needed to confirm our findings. We would also like to note that we hypothesize that other components of the program, such as team behavior and motivation, are likely to play a role in improving the ESS scores of the baseline EDS group. We are unable to determine whether the changes in health factors and ESS scores are simply concurrent reflection of successful participation in the program or causally related. In sum, this study provides a novel insight to the potential pathways through which physical activity health programs could improve daytime sleepiness. It is important to explore the causal relation of the aforementioned factors in future research with a larger sample size.

Limitations

The greatest limitation to this study was the lack of a control group. Without it, we are unable to confirm if the observed effect was due to the program. Nevertheless, our RTM analysis suggests that some of the observed immediate and sustained long-term ESS improvements in study participants with baseline EDS were likely to be due to direct effect of the program and not due to random variation and measurement error. Similarly, our RCI analysis suggests that at least half of the recoveries we observed from this study were independent of random variation. This needs to be confirmed by a controlled study.

The second limitation of this study is the potential selection bias due to the voluntary nature of study participation. Potentially, participants could have been more inclined to look after their health and hence, more likely to improve than the general population. Exclusion of data from study participants who did not complete ESS questionnaires at baseline, 4 months, and 12 months may also lead to selection bias. Returning participants were more likely to be older, have higher sedentary time, and have higher average step-count throughout the program, which have the potential to cause selection bias as some of these factors were found to be significantly associated with EDS in our previous study on the prevalence and correlates of EDS.[15] This will not affect the internal validity of this study, but it may affect the generalizability of our results. It may mean that our results are more applicable to workers with the aforementioned characteristics, which coincides with the population at high risk of obesity and NCDs.[46] Future evaluations may consider involving more participants with a greater variability in education level to provide a sample more representative of the general working population, and to include a greater number of study participants with EDS, who seem to benefit from the program.[47]

Last, ESS is the only measure of sleep in the GCC Evaluation Study. Although EDS is a common symptom from a wide range of sleep disorders and is often perceived as a general marker of poor sleep health, analysis on other sleep-related variables such as sleep duration or presence of obstructive sleep apnea would also be of interest. Inclusion of these key drivers of EDS may enhance our predictor analysis on the observed improvement in ESS.

Strengths

This is the first study to assess the immediate and sustained long-term effect of a workplace physical activity program on daytime sleepiness in a mixed population of workers. Compared with other studies that have assessed short-term associations, this study had greater power and involved study participants with greater variety of characteristics. Therefore, this study provides results that may be more applicable to the general working population. The use of measured, instead of self-reported, anthropometric data is also strength of the study.

Implications

People with greater daytime sleepiness are more likely to have accidents,[17] injuries,[18] and worse performance at work.[20] We have recently shown that one in six workers in Australia may have EDS,[15]

with a potentially higher ratio in specific high-risk groups such as shiftworkers[48] and vehicle drivers.[49] Our current findings suggest that in addition to the known benefits of improved cardiovascular health factors,[8] participation in workplace pedometer programs targeting improvement in physical activity may have concurrent immediate benefit on sleepiness, which may be maintained in the long term in people with EDS. We also found that a substantial number of study participants with baseline EDS experienced recovery from EDS at the end of program, which was sustained 8 months later. These findings are likely to be of interest to those workplaces and employers considering implementing physical activity programs through their workplaces, and those workplaces whose employees are at high risk of EDS.

CONCLUSIONS

In this evaluation of participants in a 4-month pedometer workplace health program, we found no change in daytime sleepiness in general, but a sustained improvement for those with excessive daytime sleepiness at baseline. Around one-half of those with excessive daytime sleepiness at baseline no longer had EDS immediately upon conclusion of the program. It will be important to confirm these findings in controlled studies including participants across a wide range of occupations.

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PART 2

Weight loss interventions and use of sleep medications

CHAPTER 7

Change in use of sleep medications following weight loss interventions in obese adults

"In conclusion, we found that use of hypnotics/sedatives increased following gastric bypass, and the increase continued for up to 5 years compared to intensive lifestyle treatment. After intensive lifestyle treatment, we saw no change in use of hypnotics/sedatives. Future studies need to identify the underlying mechanisms and assess whether this is observed also after other bariatric or even non-bariatric surgeries."

7.1. Summary

In the previous chapters, we have shown that weight loss interventions may improve daytime sleepiness. In this Chapter, we aimed to assess whether weight loss interventions may also improve another sleep measure, use of hypnotics and sedatives, which have been associated with obesity, potentially due to the presence of obesity-related sleep disorders. Prior to the commencement of the study, we hypothesised that use of hypnotics and sedatives may decrease after weight loss through intensive lifestyle modification, and to a greater degree, after gastric bypass surgery; because of improvements in obesity-related sleep disorders. However, to our surprise, we found an increased use of hypnotics and sedatives up to five years following weight loss through gastric bypass surgery, compared to intensive lifestyle modification. Similarly, among those who used hypnotics and sedatives at baseline, the average treatment dose (for hypnotics and sedatives) increased up to five years after gastric bypass surgery. Given the lack of a dose-response relationship between the amount of weight loss and the degree of increase in use of sleep medications, it is likely that it was not the weight loss, but something to do with the gastric bypass procedure itself that led to increased use of hypnotics and sedatives in the surgery patients. Future studies must assess the pathways through which the undertaking of gastric bypass surgery may lead to increased use of hypnotics and sedatives, and whether a similar phenomenon can be observed following other types of bariatric or non-bariatric surgeries. Regardless, a management and prevention strategy for use of hypnotics and sedatives following gastric bypass surgery is warranted, to prevent to the negative consequences of using hypnotics and sedatives from occurring.

7.2. Manuscript: Change in use of sleep medications after gastric bypass surgery or intensive lifestyle treatment in obese adults

7.2.1. Declaration

In the case of Chapter 7, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Study design, literature synthesis, statistical analysis, integrity of the data and accuracy of the data analysis, critical interpretation of the data, drafting manuscript	70%

The following co-authors contributed to the work. If co-authors are students at Monash University, the extent of their contribution in percentage terms must be stated:

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
Anna Peeters	Study design, statistical analysis, critical interpretation of the data, drafting manuscript	N/A
Ingmar Näslund	Data collection, critical interpretation of the data, drafting manuscript	N/A
Johan Ottosson	Data collection, critical interpretation of the data, drafting manuscript	N/A
Kari Johansson	Data collection, critical interpretation of the data, drafting manuscript	N/A
Claude Marcus	Critical interpretation of the data, drafting manuscript	N/A
Jonathan Shaw	Study design, criticial interpretation of the data, drafting manuscript	N/A
Gustaf Bruze	Study design, statistical analysis, integrity of the data and accuracy of the data analysis, critical interpretation of the data, drafting manuscript	N/A
Johan Sundström	Statistical analysis, critical interpretation of the data, drafting manuscript	N/A
Martin Neovius	Study design, data collection, statistical analysis, integrity of the data and accuracy of the data analysis, critical interpretation of the data, drafting manuscript	N/A

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the candidate's and co-authors' contributions to this work*.

Candidate's Signature		**Date** 17/03/2017
Main Supervisor's Signature		**Date** 17/03/2017

*Note: Where the responsible author is not the candidate's main supervisor, the main supervisor should consult with the responsible author to agree on the respective contributions of the authors.

7.2.2. Manuscript

Change in use of sleep medications after gastric bypass surgery or intensive lifestyle treatment in obese adults

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Change in use of sleep medications after gastric bypass surgery or intensive lifestyle treatment in obese adults

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ABSTRACT

Objective To examine the change in use of hypnotics/sedatives after gastric bypass surgery or intensive lifestyle modification in adults with obesity.

Methods Obese adults who underwent gastric bypass surgery or initiated intensive lifestyle modification between 2007 and 2012 were identified through the Scandinavian Obesity Surgery Registry and a Swedish commercial health database. The two cohorts were matched on body mass index (BMI), age, sex, education, history of hypnotics/sedatives use, and treatment year (surgery n=20,626; lifestyle n=11,973; 77% women, mean age 41 years, mean BMI 41kg/m^2). The proportion of participants with filled hypnotics/sedatives prescriptions was compared yearly for 3 years.

Results In the matched treatment cohorts, 4% had filled prescriptions for hypnotics/sedatives during the year before treatment. At 1 year follow-up, following an average weight loss of 37kg and 18kg in the surgery and intensive lifestyle cohorts respectively, this proportion had increased to 7% in the surgery cohort but remained at 4% in the intensive lifestyle cohort (risk ratio 1.7, 95%CI 1.4-2.1), at 2 years 11% vs 5% (risk ratio 2.0, 95%CI 1.7-2.4), and at 3 years, 14% vs 6% (risk ratio 2.2, 95%CI 1.9-2.6).

Conclusions Gastric bypass surgery was associated with increased use of hypnotics/sedatives compared to intensive lifestyle modification.

Keywords: weight loss; sleep medication; obesity; hypnotics; sedatives

Introduction

Between 1980 and 2014, the worldwide prevalence of obesity increased rapidly to 10.8% in men and 14.9% in women; in Sweden to 21.4% in men and 18.6% in women.(1) The corresponding prevalence for extreme obesity (body mass index [BMI] ≥40kg/m^2) were 0.6%, 1.6%, 0.9% and 1.5% respectively.(1) This is concerning because obesity affects various aspects of health,(2) including sleep.(3)

Obesity has been associated with sleep disorders such as obstructive sleep apnea, insomnia and restless leg syndrome.(3) Perhaps as a consequence, obese individuals have also been found to use more hypnotics/sedatives than non-obese individuals.(4) Weight loss interventions have been shown to improve a range of sleep parameters, mostly those associated with obstructive sleep apnea,(5, 6) but their effects on use of hypnotics/sedatives is unclear. This is an important area to address as use of hypnotics/sedatives have been associated with vehicle accidents,(7) fall-related injuries,(8) cognitive decline,(9) and mortality.(10)

Using Swedish nationwide and virtually complete registers we aimed to assess the effect of weight loss through gastric bypass surgery versus intensive lifestyle modification on use of hypnotics/sedatives, in obese adults. We hypothesized that use of hypnotics/sedatives would decrease following weight loss due to improvements in obesity-related sleep disorders, and to a greater degree after gastric bypass surgery than intensive lifestyle modification, due to the higher magnitude of weight loss after surgery.

What is already known about this topic?

- Severe obesity has been reported to be associated with increased use of sleep medications, potentially due to the presence of obesity-related sleep disorders such as insomnia and obstructive sleep apnea. It is unknown whether intentional weight loss through interventions such as bariatric surgery or intensive lifestyle modification may help decrease the use of sleep medications in those with severe obesity.

What does this study add?

- Contrary to our hypothesis, we found that use of sleep medications increased after gastric bypass surgery, and no change in the intensive lifestyle group. We found no evidence of a dose-response relationship between change in BMI and change in use of sleep medications in both intervention groups.

- Our findings suggest the need to monitor use of sleep medications after gastric bypass surgery. We also need to further investigate the likely pathways through which gastric bypass surgery may lead to increased use of sleep medications.

Methods

This study included individuals from the Scandinavian Obesity Surgery Registry (SOReg), which is a nationwide prospective register of bariatric surgery patients; and the Itrim health database, which is a register of individuals who underwent weight loss through a low- or very-low-calorie-diet (LCD/VLCD) with lifestyle modification.(11-14) Individuals were linked to the nationwide Swedish Prescribed Drug Register and health registers at the National Board of Health and Welfare, and Statistics Sweden, using the Swedish personal identity number, a unique identifier for each Swedish resident.

All analyses were conducted on de-identified data, and the study was approved by the regional ethics review board in Stockholm, Sweden. Participants were given possibility to opt out of the registries.

Data sources

The Scandinavian Obesity Surgery Registry (SOReg)

SOReg is a nationwide registry for patients who undergo bariatric surgery in Sweden.(13) It is currently estimated to cover approximately 99% of all bariatric surgeries, including both public and private provision. Data on various health factors, including BMI, are collected as part of clinical practice and recorded electronically.

The Itrim Health Database

The Itrim health database contains health information on participants of a commercially available intensive lifestyle modification program in Sweden. Baseline and quarterly follow-up data on various health factors, including BMI, were collected from 35 Itrim centers across Sweden, utilizing the same information technology platform.

The Prescribed Drug Register

The Prescribed Drug Register records all filled prescriptions in Sweden. It contains detailed individual-level information on the date, type and amount of prescriptions filled. We accessed data on prescriptions registered between July 1, 2005, and September 30, 2015.

Other registers

Data on age, sex, education, and emigrations were collected for each individual from the Longitudinal Integration Database for Health Insurance and Labor Market studies, the Education Register, and the Total Population Register(15) at Statistics Sweden. Data on hospital visits and deaths were available through linkage with the National Patient Register and the Causes of Death Register at the National Board of Health and Welfare.

Inclusion and exclusion criteria

We restricted the study population to individuals who were at least 18 years old, with BMI between 30 and <50kg/m^2 at the start of treatment. SOReg patients undertaking non-gastric bypass surgery were excluded (2%). As we required each individual to have prescription data from 2 years prior to 3 years after initiation of treatment, we restricted the study population to those who initiated treatment between July 1, 2007, and September 30, 2012. Individuals who emigrated after treatment initiation were excluded from the study (SOReg-n=126, Itrim-n=54).

Matching

Individuals from SOReg and Itrim were matched on treatment year and the set of covariates identified through a directed acyclic graph(16) (Supplementary Figure 1) built using Dagitty v.2.3.(17) The minimal sufficient adjustment set for producing an unbiased estimate of the total effect of bariatric surgery on sleep problems included age, sex, socioeconomic status, baseline BMI and sleep problems prior to treatment. We used data on education level as a proxy for socioeconomic status.(18)

Coarsened exact matching techniques were used, which involves categorizing values of each matching factor into substantively meaningful groups (Supplementary Table 1), upon which exact matching was performed.(19) To minimize loss of information, we allowed matching strata to include different numbers of surgery patients and intensive lifestyle modification participants.

Exposures

Patients in the surgery cohort (from SOReg) underwent gastric bypass. Participants in the intensive lifestyle treatment cohort (from Itrim) underwent a 3-month dietary weight loss phase facilitated by LCD or VLCD, followed by a 9-month weight maintenance phase (Supplementary Methods).(11) The choice of LCD or VLCD was based on the participants' baseline BMI, personal preference and contraindication status. Treatment with LCD/VLCD produces a greater degree of weight loss than other non-surgical treatments,(11, 20) and was selected as the comparator cohort due to presence of obesity and intention to lose weight.

Outcome and follow-up

The main outcome was hypnotics/sedatives prescriptions filling identified via the nationwide Prescribed Drug Register through the World Health Organization Anatomical Therapeutic Chemical (ATC) codes under N05C (Supplementary Table2). Medications were excluded if their primary indication included health conditions other than sleep problems, such as mental health disorders (Clomethiazole [N05CM02] and Valerianae radix [N05CM09]). Midazolam (N05CD08) was excluded as it is indicated for pre-operative sedation. Collectively, the excluded medications constituted 0.26% of all sleep medication prescriptions in the matched dataset throughout the entire study period.

The categorical outcome was defined as the proportion of individuals with at least 1 filled prescription of the selected medications in a given year. The continuous outcome was defined as annual mean treatment dose of hypnotics/sedatives calculated as follows:

$$\frac{\text{(Number of pills filled in a year)} \times \text{(dose per pill filled)}}{\text{Defined Daily Doses}}$$

where Defined Daily Doses (DDDs) refer to the daily dose of a particular medication recommended by the World Health Organization.(21)

Individuals were followed from treatment initiation until death or end of follow-up, whichever came first. All individuals in the current dataset had at least 3 years follow-up. We also created a second matched dataset comprising the sub-group of individuals with 5 years follow-up.

Covariates

Baseline weight and height measurements were used to calculate BMI. Poor mental health was defined as individuals with history of inpatient stays or outpatient visits for psychiatric disorders (ICD10: F00-F99), and/or prescribed medications for mental health disorders (ATC codes: N06, N05A and N05B). In the surgery cohort, information on use of continuous positive airway pressure (CPAP) was obtained during clinical examination at baseline. History of inpatient stays and outpatient visits for any cause were identified through the National Patient Register, and prescription history from the Prescribed Drug Register.

Statistical analysis

We compared the proportion of individuals with filled hypnotics/sedatives prescriptions post-treatment in the surgery and intensive lifestyle cohorts using a generalized linear model with log link, assuming a binomial distribution (or Poisson in the event of non-convergence). Analyses were also performed using linear regression to estimate the mean between-cohort difference in annual treatment dose in individuals with filled hypnotics/sedatives prescriptions prior to treatment. All analyses were weighted to take into account the different sizes of matching strata.

Subgroup analysis

Subgroup analyses and treatment interaction tests were performed by baseline age, sex, education level, BMI, and mental health status.

Within group analysis

To assess dose-response relationship between BMI change and outcomes, we repeated the analyses comparing outcomes by tertiles of 1-year %BMI change separately for the surgery and the intensive lifestyle cohorts. In the surgery cohort, we also investigated the outcome in patients with versus without CPAP at baseline (CPAP use data not available in the intensive lifestyle cohort).

Sensitivity analysis

We repeated the main analysis in the matched dataset, additionally adjusting for the original matching variables (continuous age, continuous BMI, cumulative DDDs within 2 years prior to treatment, and treatment year), indicators of poor mental health, and history of health care contacts from 1 year to 2 years prior to treatment (measured through history of inpatient stays, outpatient visits and filled prescription for any medications). Health care contacts in the year immediately prior to treatment (from 0 to 1 year prior to treatment) were not considered because they may be unusually high during that year, especially in the surgery cohort.

All analyses were performed using SAS version 9.4 and STATA version 14. A statistically significant finding was defined as a two-sided P-value of <0.05.

Results

Study population

Before matching, there were 24,291 individuals in the surgery cohort, and 13,095 individuals in the intensive lifestyle treatment cohort. After matching, the numbers were 20,626 (85% of starting sample) and 11,973 (91% of starting sample) respectively (Supplementary Figure 2).

Baseline characteristics

Before matching, surgery patients were more likely to be younger, have lower education, higher BMI, and have filled hypnotics/sedatives prescriptions than intensive lifestyle participants. After matching, discrepancies across treatment cohorts were no longer detected, except for BMI which remained 0.5kg/m^2 (95%CI 0.4-0.6; P<0.001) higher in the surgery than the intensive lifestyle cohort (Table 1). In the matched sample, surgery patients were also more likely to have poor mental health and have had health care contacts prior to treatment compared to the intensive lifestyle participants.

Weight loss and hypnotics/sedatives use after surgery and intensive lifestyle modification

The mean 1-year weight loss was 37kg in the surgery and 18kg in the intensive lifestyle cohort (mean difference 19kg, 95%CI 18-20; P<0.001). The three most commonly prescribed hypnotics/sedatives were zopiclone, zolpidem and propiomazine, accounting for 96% of all prescriptions in both treatment cohorts throughout the study period (Supplementary Table 2 and Supplementary Figure 3).

During follow-up, the risk of having filled hypnotics/sedatives prescriptions was higher in the surgery than the intensive lifestyle cohort, and the risk ratio increased with longer follow-up, peaking at 3 years (risk ratio 2.2, 95%CI 1.9-2.6; P<0.001; Figure 1). In the second matched dataset the proportion continued to increase up to 5 years of follow-up (Figure 1).

Among those with filled hypnotics/sedatives prescriptions prior to treatment, mean treatment dose increased more in the surgery than the intensive lifestyle cohort with a mean difference at 3 years of 57 DDDs (95%CI 39-75; P<0.001; Figure 2). In the second matched dataset the mean difference continued to increase up to 5 years of follow-up (Figure 2).

Adjustment for the original matching variables prior to categorization (Supplementary Table 1) and/or indicators of poor mental health and/or history of health care contacts before treatment resulted in ≤0.2 change for risk ratios and ≤2 DDD change for mean differences which remained statistically significant at all time-points.

Subgroup analyses

In 12 out of 14 subgroups, surgery patients were at greater risk of having filled hypnotics/sedatives prescriptions than intensive lifestyle participants during follow-up (Figure 3). Within each level of educational attainment, the risk was increased in the surgery compared to the intensive lifestyle cohort. We found a statistically significant interaction by baseline BMI but the direction was not clear.

In individuals with filled hypnotics/sedatives prescriptions prior to baseline, we did not find any treatment-subgroup interactions regarding dose, potentially due to low power (Figure 3).

Within group analysis

%BMI change: No dose-response relationship was found for 1-year %BMI change and the outcome in either the surgery or the intensive lifestyle cohort (Figure 4).

Baseline use of CPAP (surgery only): The risk of having filled hypnotics/sedatives prescriptions 3 years after treatment did not differ by baseline use of CPAP. Among those with filled hypnotics/sedatives prescriptions at baseline, mean treatment dose increased more in patients without than with CPAP at baseline (Figure 4).

DISCUSSION

We found higher use of hypnotics/sedatives following gastric bypass compared to intensive lifestyle modification during 3 and 5 years follow-up, and this difference was present in 12 out of 14 subgroups investigated. There was no evidence in either treatment cohort for a dose-response relationship between %BMI change at 1 year and change in use of hypnotics/sedatives at 3 years.

Our finding of an increased use of hypnotics/sedatives after gastric bypass is consistent with that from an uncontrolled 2-year follow-up study of 165 Norwegian patients,(22) and from a Swedish study comparing matched cohorts of 3,139 gastric bypass patients with 31,390 general population controls over 4 years follow-up.(23) Note that the Swedish study did not match for baseline BMI.

Since we did not find evidence for a dose-response relationship between %BMI change and change in use of hypnotics/sedatives, nor any change after substantial non-surgically induced weight loss, it is likely that the increased use was driven by the undertaking of gastric bypass surgery, and not by weight loss per se. While we cannot identify the cause of this phenomenon through our study, a number of plausible explanations can be identified in the literature. One possibility is “addiction transfer” whereby patients stop overeating for anxiety relief but acquire other compulsive disorders such as alcoholism or substance abuse after bariatric surgery.(24) The mechanism is unclear, and whether compulsive eating behavior prior to surgery can be considered as ‘addiction’ remains debatable,(25) but this phenomenon is continually being reported in bariatric surgery patients.(24)

Another plausible explanation is that gastric bypass increases the risk of alcoholism and substance abuse,(26-29) which in turn leads to poor sleep.(30, 31) Malabsorption after gastric bypass may explain increased mean treatment dose among baseline users, but not the uptake of new users post-surgery.(32) One could also argue that hypnotics/sedatives use could increase after surgery due to patients having more frequent contact with clinicians at follow-up than intensive lifestyle participants. However, this is unlikely to be the full explanation given the continuous uptake of new users even at 3-5 years follow-up, when health care contacts for post-operative care have presumably decreased.

In the presence of obstructive sleep apnea, most hypnotics/sedatives are to be used with caution.(33, 34) It is possible that following substantial improvement in severity of obstructive sleep apnea post bariatric surgery (recently shown in another study using SOReg data(35)), as use of hypnotics/sedatives is no longer contraindicated, clinicians started to prescribe (more) hypnotics/sedatives for the surgery patients to treat residual sleep problems. If this was the case, we should observe a greater increase in hypnotics/sedatives prescription fillings among baseline CPAP users than in those without CPAP. We found instead a lower mean treatment dose at 3 years post-surgery among CPAP users than in those without CPAP at baseline, although both cohorts increased their use compared to baseline. Also, at baseline use of hypnotics/sedatives did not differ between those with and without CPAP. It seems that despite warnings in the medication label, hypnotics/sedatives are still often used in patients with CPAP, potentially to aid with sleep and improve compliance.(36-39) A recently published study, also using SOReg data have shown that use of CPAP decreased following gastric bypass surgery, over 5 years follow-up.(35)

Our study utilized nationwide registry data, which implies minimum loss to follow-up for the outcome (0.5% due to emigrations), large sample size, and high generalizability within the Swedish population, which is predominantly Caucasian. Use of hypnotics/sedatives was assessed through filled prescriptions recorded in the Prescribed Drug Register, providing better accuracy than self-reported data. We included participants in an intensive lifestyle modification program as our comparator cohort, which addressed previous concerns over lack of studies on bariatric surgery with comparators producing sufficient weight loss.(40) The average

magnitude of 1-year weight loss from the intensive lifestyle cohort in this study (18kg) is substantially larger than other conventional treatment comparators in previous bariatric surgery studies (max 8kg).(20)

There are several limitations to this study. Even though we minimized the overlap between sleep and mental health problems by excluding medications with shared indications for mental health problems, we cannot control the off-label use of the remaining medications, and there are often more than one reason to prescribe a certain medication. Nevertheless, even if use of hypnotics/sedatives is not a perfect marker for sleep problems, our finding of increased hypnotics/sedatives after bariatric surgery remains a clinically important observation. Also, our estimates were robust to adjustments for baseline mental health.

This study was not a randomized controlled trial, and is therefore prone to confounding. We attempted to minimize confounding by matching on covariates identified through a directed acyclic graph, but we cannot prove if our diagram is true and complete. There may be other inherent (personality) differences between the surgery and intensive lifestyle treatment cohorts that we do not capture, which may contribute to the observed differences. For instance, before matching intensive lifestyle participants had higher level of education, likely representing a more health-conscious population who may be more resistant to pharmacological aid such as hypnotics/sedatives. In our analysis, we aimed to capture this difference in 'health-seeking behavior' between the treatment cohorts through adjusting for history of health care contacts, and the estimates changed ≤0.2 for risk ratios and ≤2 DDDs for mean differences, but this may not be sufficient. However, surgery increased the risk of having filled hypnotics/sedatives prescriptions compared to intensive lifestyle in all education level subgroups.

The surgery cohort in our current study only included gastric bypass. Our result may not be generalizable to other procedure types.

CONCLUSION

In conclusion, we found that use of hypnotics/sedatives increased following gastric bypass, and the increase continued for up to 5 years compared to intensive lifestyle treatment. After intensive lifestyle treatment, we saw no change in use of hypnotics/sedatives. Future studies need to identify the underlying mechanisms and assess whether this is observed also after other bariatric or even non-bariatric surgeries. Our findings indicate the need for sleep drug monitoring and management following gastric bypass, to prevent uptake of new users and continuous increase in mean treatment dose of hypnotics/sedatives after gastric bypass.

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Disclosure

IN is the previous director of the Scandinavian Obesity Surgery Registry. JO is the current director. CM, MN and JSund report receiving consulting fees for participation in the scientific advisory committee of Itrim. Further, MN has received research grants from Pfizer, Cambridge Weight Plan, Novo Nordisk and Astra Zeneca; royalty payments from Studentlitteratur for co-authoring chapters in a Swedish textbook on obesity; and lecture or consulting fees from Pfizer, Sanofi-Aventis, Roche and Strategic Health Resources. AP and JShaw have participated in a Novo Nordisk advisory board.

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Table 1 Baseline characteristics

Matching factors	Before matching			After matching		
	Surgery (n=24,291)	Intensive lifestyle (n=13,095)	Mean difference or risk ratio (95%CI)	Surgery (n=20,626)	Intensive lifestyle (n=11,973)	Mean difference or risk ratio (95%CI)
Mean age (years)	41.3 (10.9)	46.0 (12.0)	-4.7 (-5.0 to 4.5)	41.2 (10.7)	41.3 (11.1)	-0.1 (-0.3 to 0.0)
Men, n (%)	5,715 (23.5)	3,071 (23.5)	1.0 (1.0 - 1.0)	4,791 (23.2)	2,781 (23.2)	*Exactly matched*
University education, n (%)	5,173 (21.4)	6,203 (47.6)	0.4 (0.4 - 0.5)	4,514 (21.9)	2,620 (21.9)	*Exactly matched*
Mean BMI at screening (kg/m^2)	41.5 (4.0)	34.5 (3.8)	7.0 (6.9 - 7.1)	41.4 (4.0)	40.9 (4.2)	0.5 (0.4 - 0.6)
Filled hypnotics/sedatives prescriptions 0-1 year pre-treatment, n (%)	3,543 (14.6)	1,185 (9.1)	1.6 (1.5 - 1.7)	826 (4.0)	479 (4.0)	*Exactly matched*
Mean treatment dose (DDD)	317 (452)	188 (313)	129 (101 - 156)	70 (91)	67 (90)	3 (-1 to 7)
Filled hypnotics/sedatives prescriptions between 1-2 years pre-treatment, n (%)	3,529 (14.6)	1,174 (9.0)	1.6 (1.5 - 1.7)	883 (4.3)	513 (4.3)	*Exactly matched*
Mean treatment dose (DDD)	288 (429)	190 (352)	97 (70 - 124)	65 (83)	66 (84)	0 (-5 to 4)
Other covariates						
Use of continuous positive airway pressure, n (%)	2,223 (9.2)	NA	NR	1,831 (8.9)	NA	NR
Indicators of poor mental health, n (%)	7,187 (29.6)	2,293 (17.5)	1.7 (1.6 - 1.8)	4,797 (23.3)	1,806 (15.1)	1.5 (1.4 - 1.7)
Health care contacts 1-2 years pre-treatment						
Outpatient visits, n (%)	14,289 (58.8)	5,136 (39.2)	1.5 (1.5 - 1.5)	11,609 (56.3)	4,737 (39.6)	1.4 (1.3 - 1.5)
Inpatient stays n (%)	3,483 (14.3)	1,274 (9.7)	1.5 (1.4 - 1.6)	2,688 (13.0)	1,238 (10.3)	1.3 (1.1 - 1.4)
Filled prescription for any medications, n (%)	21,778 (89.7)	10,577 (80.8)	1.1 (1.1 - 1.1)	18,241 (88.4)	9,751 (81.4)	1.1 (1.1 - 1.1)

All mean values are presented with standard deviations
Mean difference is for continuous variables and risk ratio is for categorical values
All data were weighted to take into account different sizes of matching strata
Abbreviations: BMI, Body mass index; DDDs, Defined daily doses; NA, Not available; NR, Not relevant
Indicators of poor mental health: Inpatient stay or outpatient visit listing a mental health diagnosis, or filled prescriptions for mental health indications
The proportions of individuals with filled hypnotics/sedatives prescriptions stratified by levels of matching factors in the unmatched dataset are shown in Supplementary Figure 6

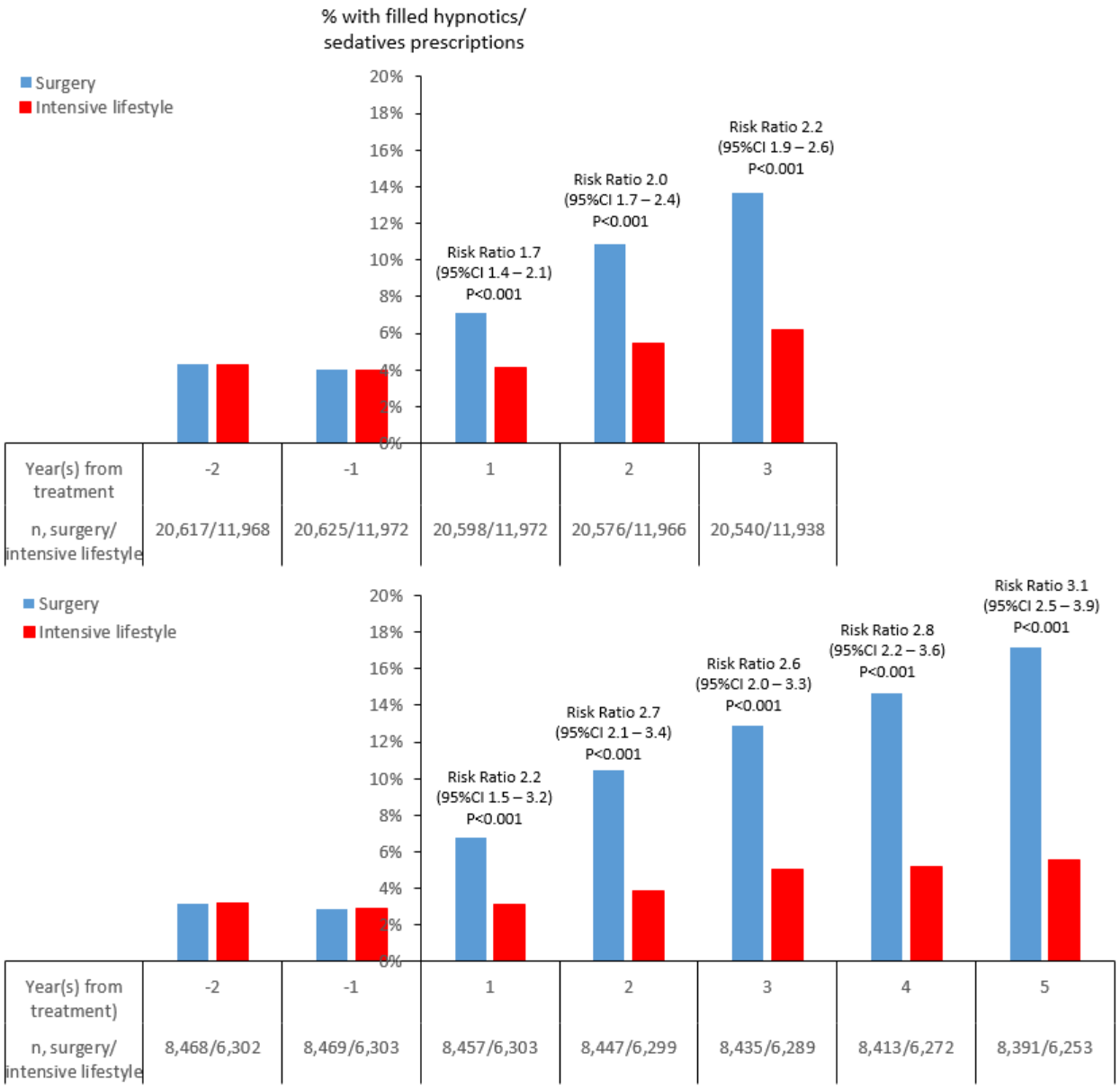


Figure 1 Proportion with filled hypnotics/sedatives prescriptions in the matched study population with 3 years follow-up (upper panel) and in the sub-group with 5 years follow-up period (lower panel)

Risk ratios (95%CI) apply to the between cohort differences at each follow-up time point

Baseline characteristics of subgroup with 5 years follow-up shown in Supplementary Table 3

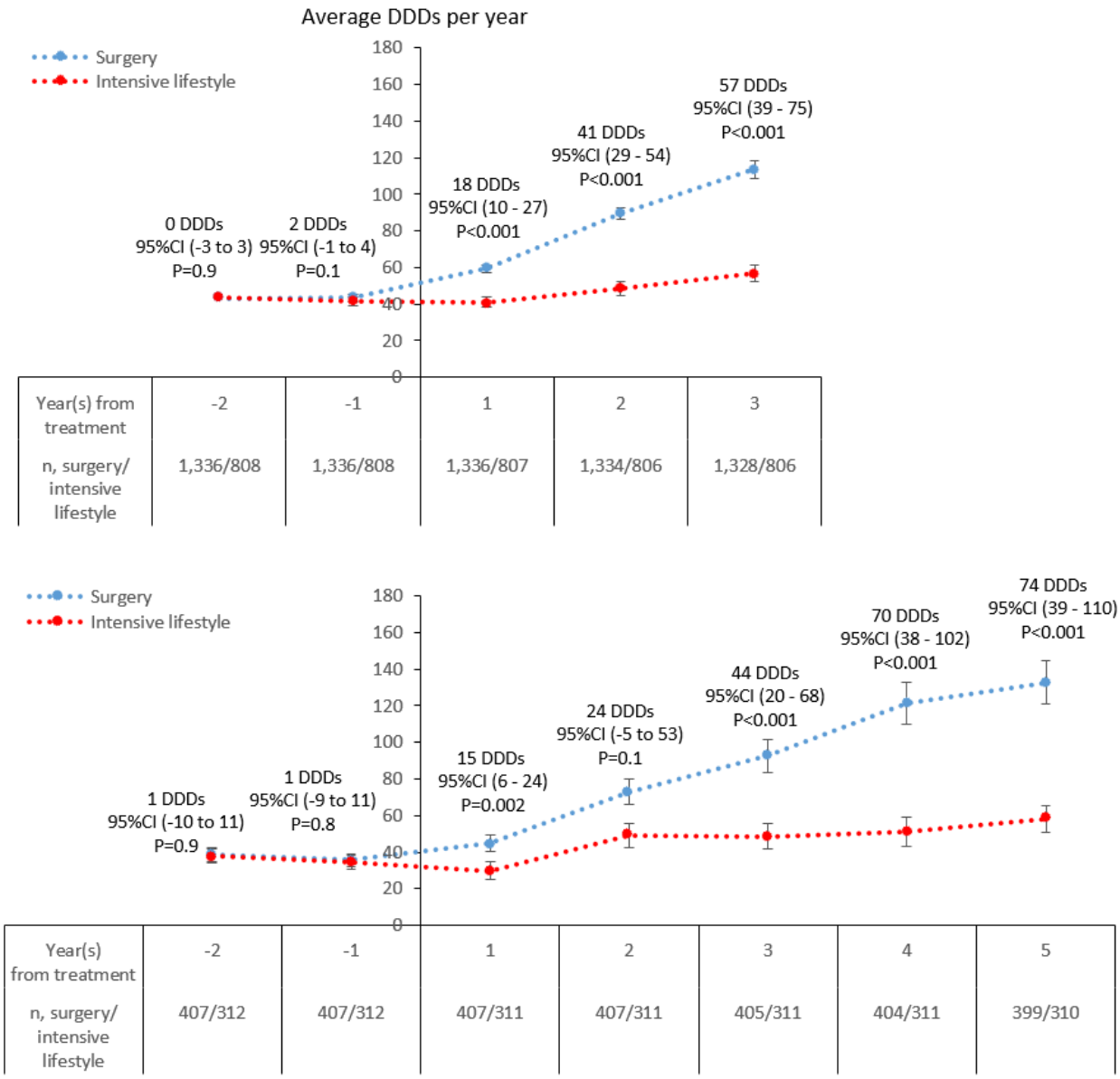


Figure 2 Mean treatment dose among those with filled hypnotics/sedatives prescriptions at 1 and/or 2 years prior to treatment, in the matched study population with 3 years follow-up (upper panel) and in the sub-group with 5 years follow-up (lower panel)

Error bars are 95%CI

Mean differences (95%CI) apply to the between cohort differences at each follow-up time point

Baseline characteristics of subgroup with 5 years follow-up shown in Supplementary Table 3

Abbreviations: DDDs, Defined daily doses

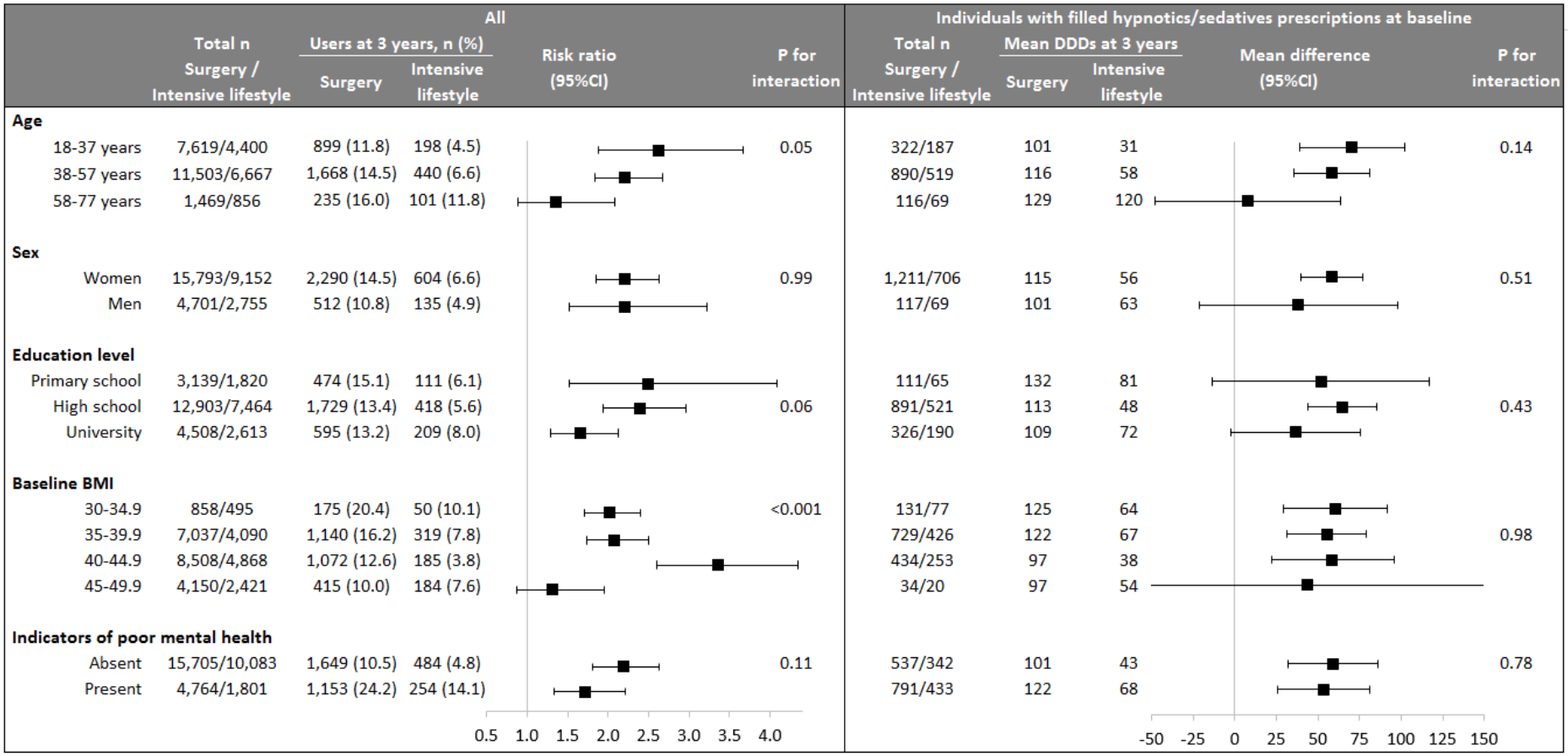
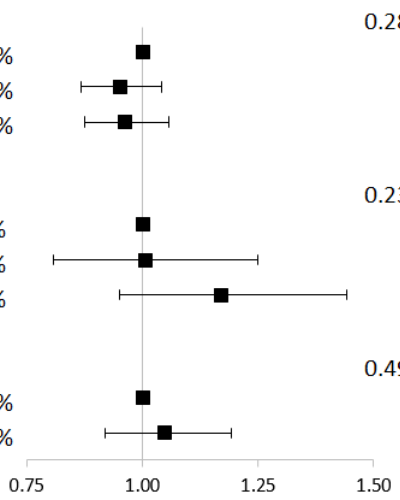
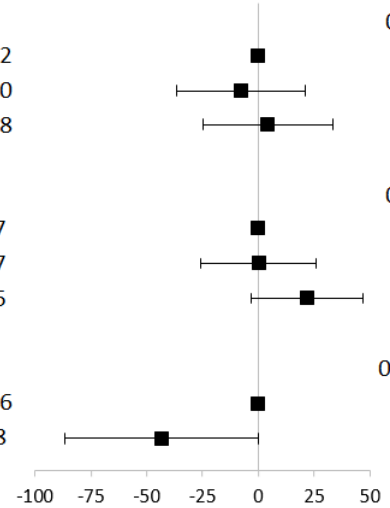


Figure 3 Use of hypnotics/sedatives in the two treatment cohorts at three-years follow-up, stratified by baseline characteristics, categorically in the overall matched study population (left) and continuously among those with filled hypnotics/sedatives prescriptions at 1 and/or 2 years prior to treatment (right)

Abbreviations: BMI, Body mass index; DDDs, Defined daily doses

	All					Individuals with filled hypnotics/sedatives prescriptions at baseline				
	n	% Users Baseline	% Users Year 3	Risk Ratio*# (95%CI)	P	n	Mean DDDs Baseline	Mean DDDs Year 3	Mean Difference* (95%CI)	P
1-year %BMI change										
Surgery					0.28					0.60
Largest (-57.9% to -34.9%)	6,104	3.3%	13.4%			342	38	102		
Medium (-34.9 to -28.4%)	6,093	3.9%	13.1%			392	42	100		
Smallest (-28.4% to 3.5%)	6,083	4.9%	13.4%			450	48	118		
Intensive lifestyle					0.23					0.13
Largest (-44.8% to -16.7%)	2,514	3.3%	5.9%			136	44	57		
Medium (-16.7% to -10.2%)	5,495	4.6%	6.5%			158	50	57		
Smallest (-10.2% to 13.2%)	2,507	4.4%	7.4%			165	54	85		
Use of CPAP pre-surgery					0.49					0.049
No	18,794	4.0%	13.6%			1,236	43	116		
Yes	1,831	3.9%	14.0%			100	49	78		





*adjusted for baseline age, sex, education and cumulative DDDs prior to treatment

#Poisson distribution assumed

Figure 4 Within treatment cohort analysis of the relationship of BMI change and of pre-surgical use of CPAP on the categorical outcome (with filled hypnotics/sedatives prescriptions, Yes/No) in the overall matched study population (left) and for the continuous outcome (mean treatment dose, DDDs) among those with filled hypnotics/sedatives prescriptions at 1 and/or 2 years prior to treatment (right)

Abbreviations: BMI, Body mass index; CPAP, Continuous positive airway pressure; DDDs, Defined daily doses

Supplementary Appendix

Change in use of sleep medications after gastric bypass surgery or intensive lifestyle treatment in obese adults

Winda L. Ng, Anna Peeters, Ingmar Näslund, Johan Ottosson, Kari Johansson, Claude Marcus, Jonathan E. Shaw, Gustaf Bruze, Johan Sundström, Martin Neovius

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Supplementary Methods The intensive lifestyle modification program

The 3-month weight loss phase of the intensive lifestyle modification program was facilitated by LCD/VLCD meal replacement therapy.

- LCD: Total daily caloric intake of 1200-1500kcal for 3-10 weeks, acquired through 2 calorie-restricted normal food meals and 2x125kcal formula-diet meal replacement sachets
- VLCD: Total daily caloric intake of 500 kcal for 3-10 weeks, acquired through 4x125kcal formula-diet meal replacement sachets (approved as sole source VLCD by the Swedish National Food Agency); after which normal food was gradually introduced during 2-8 weeks. Earlier initiation of normal food was possible if participants were satisfied with the amount of weight lost or if BMI fell below 25kg/m^2.

The 9-month weight maintenance phase that follows included an exercise program (circuit training at the center 2-3 times/week for 30-45 minutes, and pedometer use to encourage walking) and dietary advice. There were 1 hour group sessions at weekly intervals during the weight loss phase; and 2-12 sessions during the weight maintenance phase, depending on types of subscriptions, to provide support for behavioral change. Face-to-face counseling sessions were also available during the program.

Supplementary Table 1 Coarsened exact matching: Categorization of the matching variables

Variable	Description
Age	From continuous variable, divided to 8 categories with 10 years interval
Sex	Men, women
Education	Categorical variable (Primary school, high school, university)
Body mass index	Categorical variable, with 5 kg/m^2 bin, from 30 kg/m^2 to 49.9 kg/m^2
Prescribed dose of hypnotics/sedatives within 1 year prior to treatment	From continuous variable, divided into those with 0 DDD and categories with 90 DDDs interval
Prescribed dose of hypnotics/sedatives between 1-2 years prior to treatment	From continuous variable, divided into those with 0 DDD and categories with 90 DDDs interval
Treatment year	Categorized to two groups: 2007-2008, and 2009-2012

Abbreviations: DDDs, Defined Daily Doses

Supplementary Table 2 List of chemical subgroups of hypnotics and sedatives, included (a) /excluded (b) from the study

a) Included	%total number of prescriptions throughout study period
N05CD02 (Nitrazepam)	0.97%
N05CD03 (Flunitrazepam)	0.47%
N05CD05 (Triazolam)	0.10%
N05CF01 (Zopiclone)	41.47%
N05CF02 (Zolpidem)	30.06%
N05CF03 (Zaleplon)	0.85%
N05CH01 (Melatonin)	1.85%
N05CM06 (Propiomazine)	24.02%

*in matched study population with three years follow-up

b) Excluded	Reasons for exclusion	% total number of prescriptions throughout study period*
N05CC01 (Chloral hydrate)	Not registered for use in Sweden	-
N05CD08 (Midazolam)	Indicated for pre-operative sedation	0.03%
N05CM02 (Clomethiazole)	Also indicated for anxiety or agitation	0.15%
N05CM09 (Valerianae radix)	Also used for anxiety	0.03%
N05CX	Not registered for use in Sweden	-

*in matched study population with 3 years follow-up

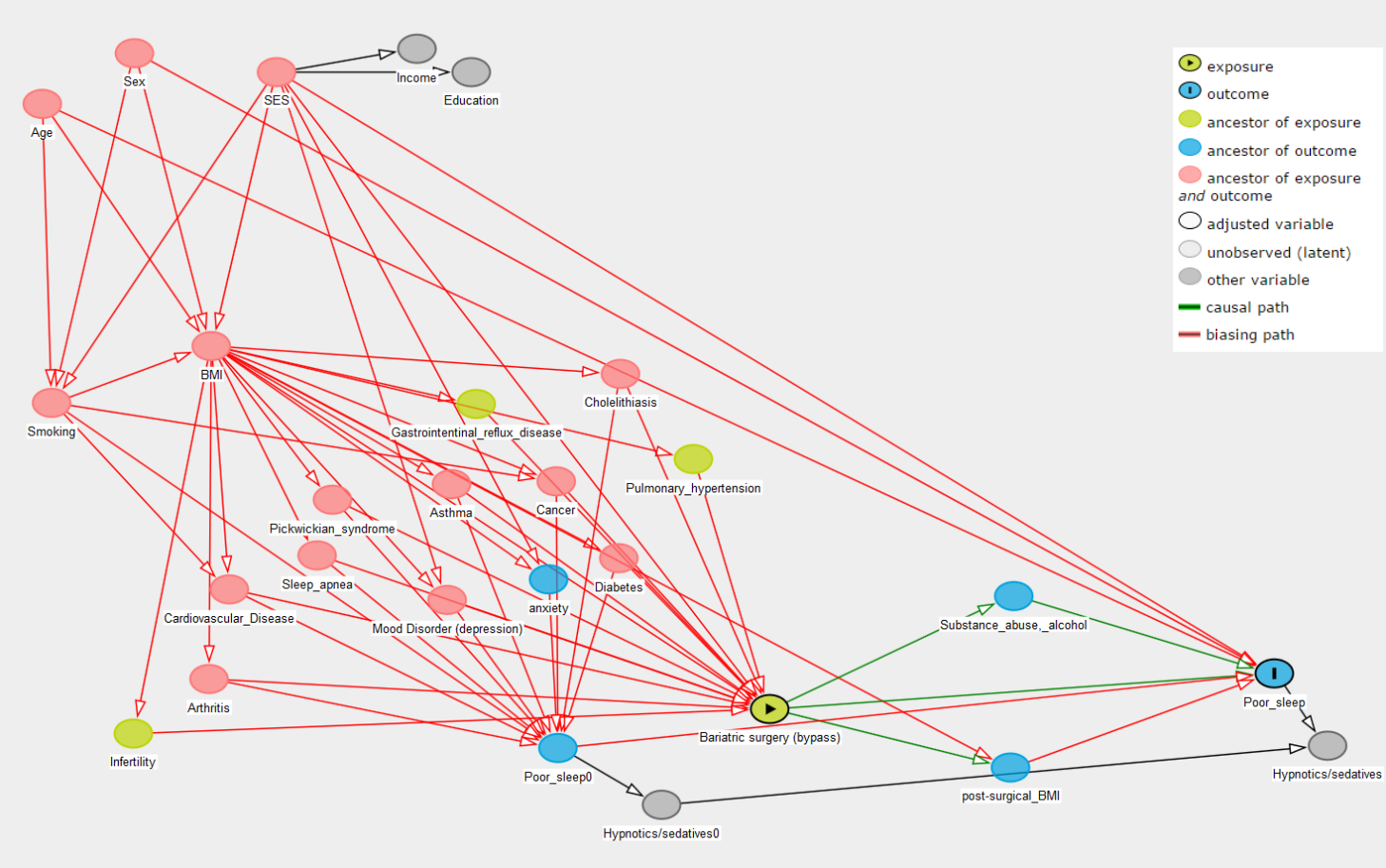
Supplementary Table 3 Baseline characteristics of the subgroup with 5 years follow-up before and after matching

	Before matching		After matching	
	Surgery (n=10,603)	**Intensive lifestyle (n=7,064)**	**Surgery (n=8,469)**	**Intensive lifestyle (n=6,303)**
Mean age (years)	41.3 (10.7)	46.7 (11.8)	40.9 (10.4)	41.0 (10.7)
Men, n (%)	2,460 (23.2)	1,556 (22.0)	1,891 (22.3)	1,407 (22.3)
University education, n (%)	2,318 (22.0)	3,399 (48.3)	1,943 (23.0)	1,446 (23.0)
Mean BMI at screening (kg/m^2)	41.6 (4.1)	34.5 (3.8)	41.5 (4.1)	40.9 (4.2)*
Filled hypnotics/sedatives prescriptions				
0-1 year pre-treatment, n (%)	1,643 (15.5)	673 (9.6)	246 (2.9)	183 (2.9)
1-2 years pre-treatment, n (%)	1,650 (15.6)	645 (9.2)	271 (3.2)	202 (3.2)

*p<0.001

All mean values are presented with standard deviations

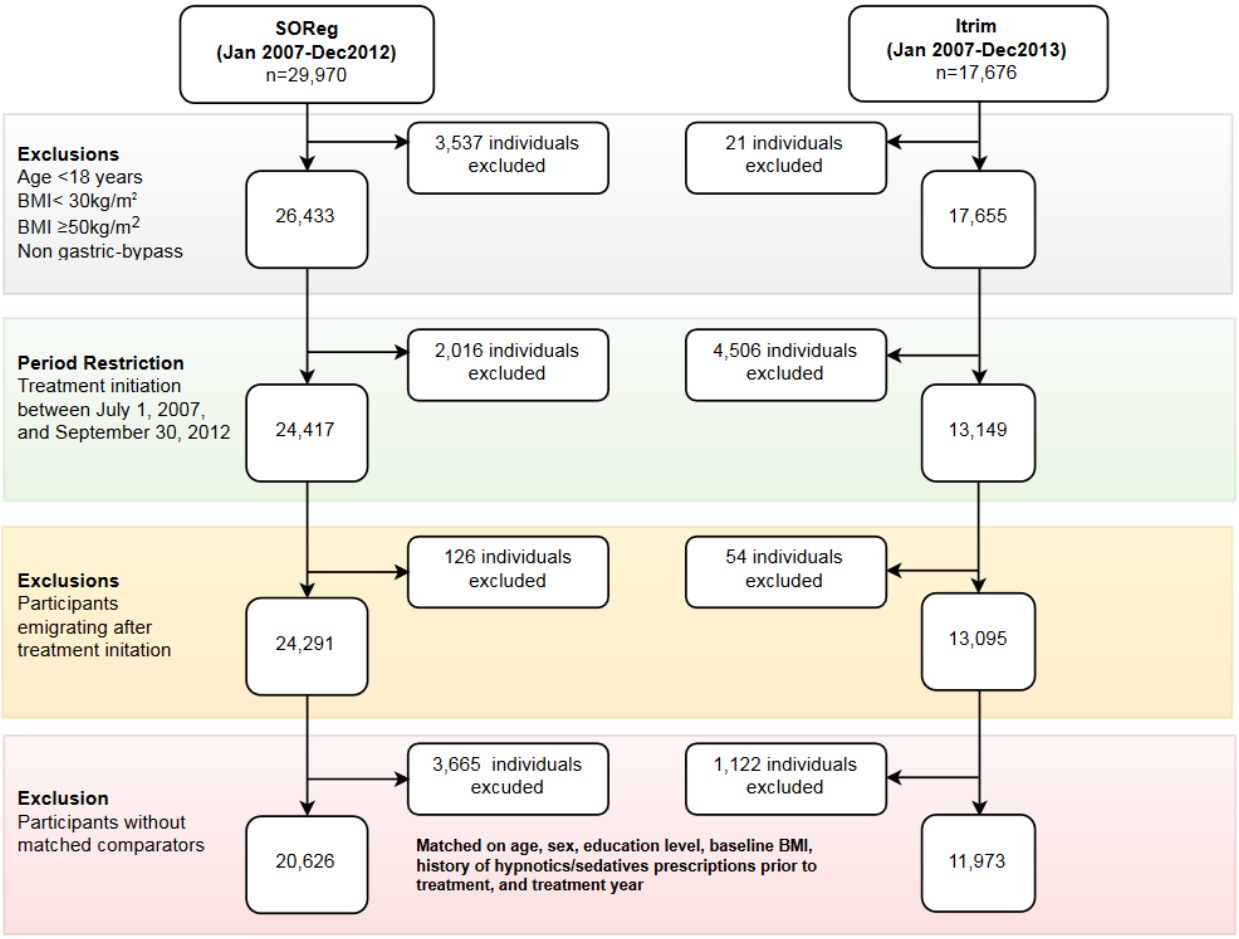
Abbreviations: BMI, Body mass index



Supplementary Figure 1 The Directed Acyclic Graph

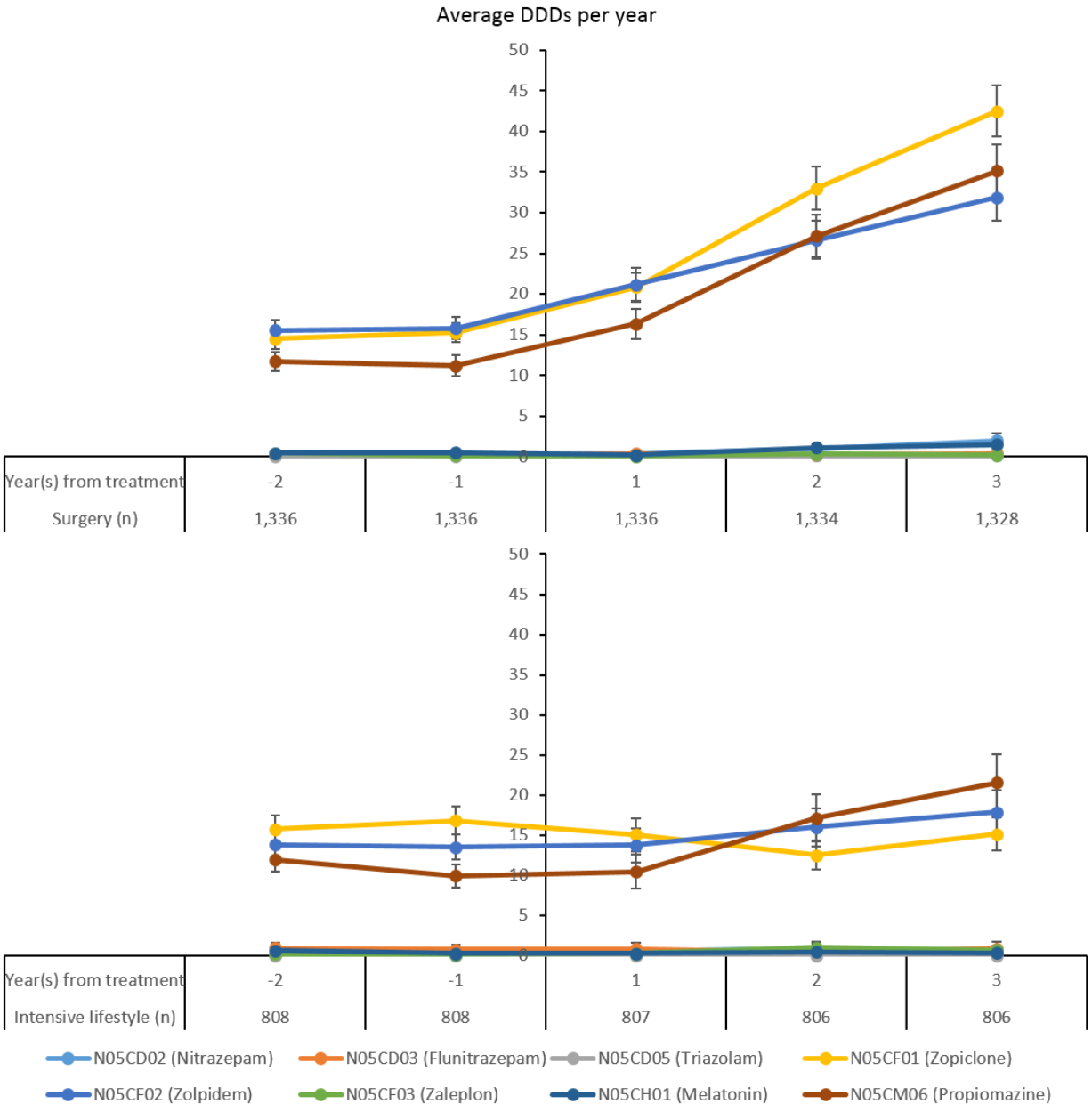
Note: The current directed acyclic graph was built based on eligibility criteria for bariatric surgery established by the National Institutes of Health in 1992. The minimum sufficient adjustment set for estimating the total effect of bariatric surgery on poor sleep is age, sex, socioeconomic status, body mass index and poor sleep.

The diagram was built using DAGitty[19]. Abbreviations: BMI, Body mass index; SES, Socioeconomic status.



Supplementary Figure 2 Flowchart summarizing the inclusion and exclusion of individuals in the study population

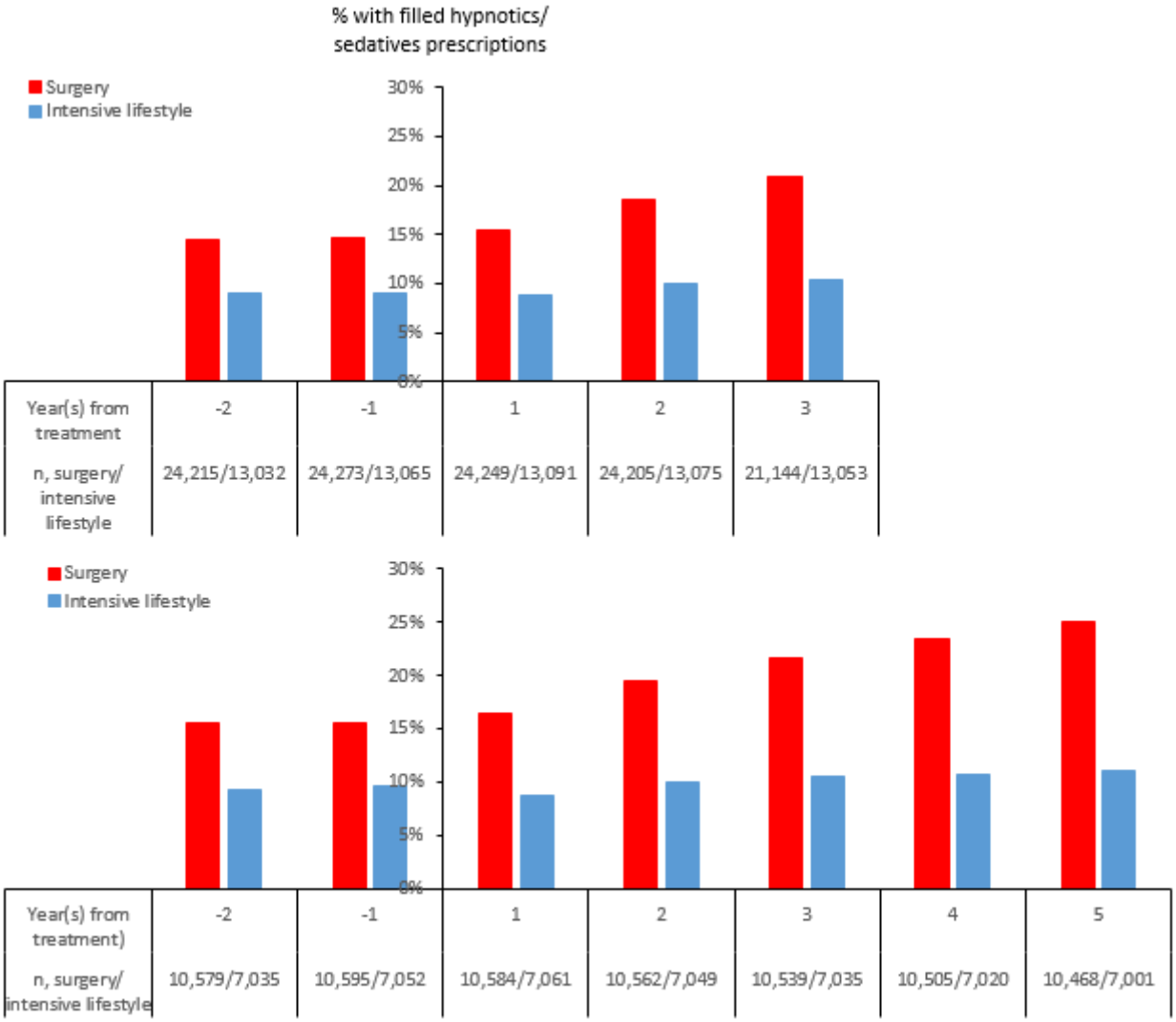
Abbreviations: BMI, Body mass index; SOReg, Scandinavian Obesity Surgery Registry



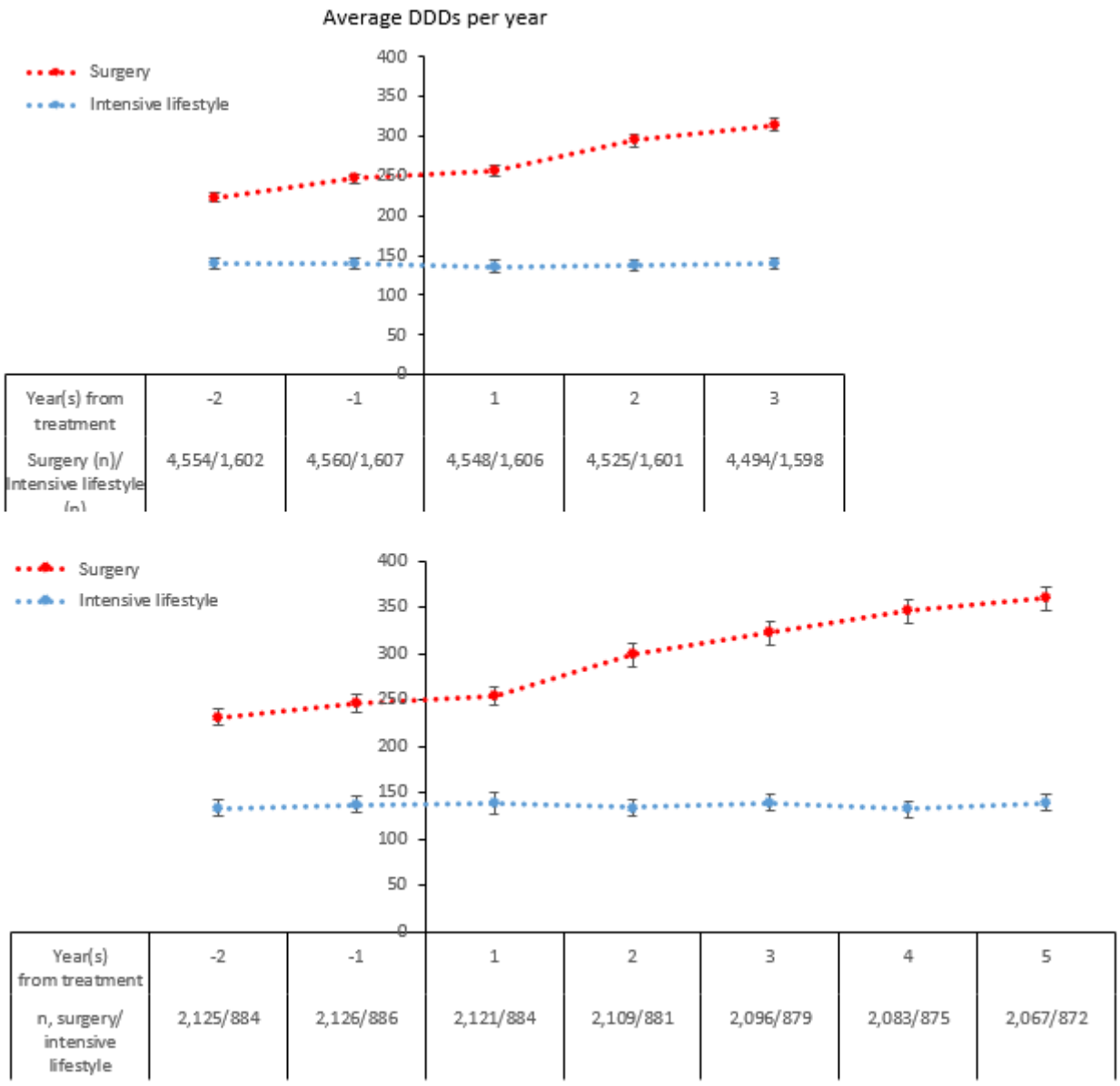
Supplementary Figure 3 Distribution of hypnotics and sedatives in the surgery cohort (upper panel) and the intensive lifestyle cohort (lower panel)

Error bars are 95%CI

Abbreviations: DDDs, Defined daily doses



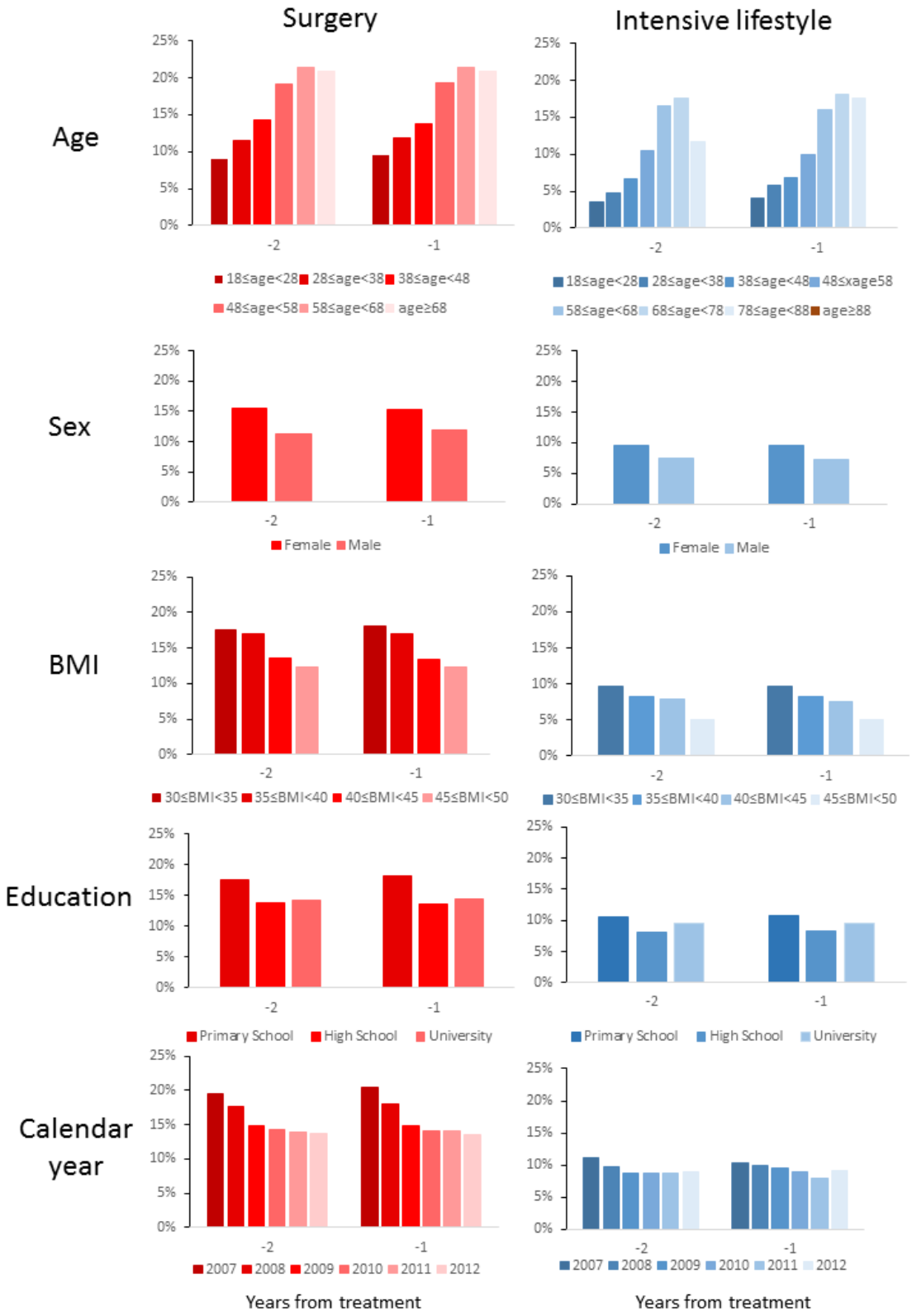
Supplementary Figure 4 Proportion with filled hypnotics/sedatives prescriptions in the unmatched dataset with 3 years follow-up (upper panel) and 5 years follow-up (lower panel)



Supplementary Figure 5 Mean treatment dose among those with filled hypnotics/sedatives prescriptions at 1 and/or 2 years prior to treatment initiation, in the unmatched study population with 3 years follow-up (upper panel) and 5 years follow-up (lower panel)

Error bars are 95% confidence intervals

Abbreviations: DDDs, Defined daily doses



Supplementary Figure 6 Proportion with filled hypnotics/sedatives prescriptions within surgery and intensive lifestyle cohorts by levels of matching factors 1 and 2 years prior to treatment initiation, in the unmatched dataset

Abbreviations: BMI, Body mass index

PART 3

The mortality and morbidity burden associated with excessive daytime sleepiness

CHAPTER 8

Sleep health, disability, mortality, and life expectancy

"EDS is associated with increased risk of mortality, higher likelihood of having disability, as well as 3 years shorter overall life expectancy and 3 years shorter disability-free life expectancy, at age 60. It is not only important to treat the underlying cause of EDS but also to manage EDS to avoid its associated burden of disease later in life."

8.1. Summary

Sleep is an underrecognised health factor in society, despite its known consequnces on our health, well-being, and quality of life. Through this study, we aimed to assess the likelihood of developing disability and the mortality risk associated with having excessive daytime sleepiness, a common complaint in both sleep clinics and the general population. The implications of the relationship between disability, mortality, and excessive daytime sleepiness on life expectancy (with and without disability) were also assessed. Using the Wisconsin Longitudinal Study, we found that in a cohort of non-hispanic, highly educated, white individuals, having chronic excessive daytime sleepiness increases the likelihood of developing disability by 1.48 times (with full adjustment for underlying medical conditions such as asthma, diabetes, and hypertension). Similarly, the risk of mortality was increased by 1.36 times in those with EDS compared to those without. Further, for individuals at age 60, excessive daytime sleepiness was associated with loss of 3 years overall life expectancy and 3 years disability-free life expectancy. In this study, we were unable to determine whether excessive daytime sleepiness may cause disability or increase the risk of mortality, independently of the underlying medical conditions; although we hypothesised that it may be due to reduced physical activity, or more rarely, through accidents and injuries. Our results provide information on the burden associated with having a relatively common sleep problem, in a form that is meaningful to the general public and practitioners alike.

8.2. Manuscript: The relationship between excessive daytime sleepiness, disability, and mortality, and implications for life expectancy

8.2.1. Declaration

In the case of Chapter 8, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Study design, literature synthesis, statistical analysis, integrity of the data and accuracy of the data analysis, critical interpretation of the data, drafting manuscript	80%

The following co-authors contributed to the work. If co-authors are students at Monash University, the extent of their contribution in percentage terms must be stated:

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
Jonathan Shaw	Study design, statistical analysis, criticial interpretation of the data, drafting manuscript	N/A
Anna Peeters	Study design, statistical analysis, integrity and accuracy of the data analysis, critical interpretation of the data, drafting manuscript	N/A

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the candidate's and co-authors' contributions to this work*.

Candidate's Signature	[redacted]	**Date** 17/03/2017
Main Supervisor's Signature	[redacted]	**Date** 17/03/2017

8.2.2. Manuscript

The relationship between excessive daytime sleepiness, disability, and mortality, and implications for life expectancy

Ng W.L., Peeters A., Naslund I., Ottosson J., Johansson K., Marcus C., Shaw J.E., Bruze G., Sundstrom J., Neovius M.

The relationship between excessive daytime sleepiness, disability, and mortality, and implications for life expectancy

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ABSTRACT

Objective To assess the relationship between excessive daytime sleepiness (EDS), disability, mortality, and life expectancy (with and without disability) in a cohort of middle-aged American adults.

Methods The Wisconsin Longitudinal Study, a life-course study on 10,317 high school graduates from Wisconsin, was used to assess the odds ratio (OR) between EDS in 2004 with prevalent and incident disability to 2011 through multiple logistic regression, and to estimate the hazard ratio (HR) of EDS in 2004 for mortality over 10 years through a Cox proportional hazard model. US 2004 population age and sex-specific rates for mortality and disability obtained from nation-wide surveys were combined with age-, sex- and EDS-specific mortality rates and disability prevalence estimated from our study to construct Sullivan life tables for those with and without EDS. Life expectancy (total, with, and without disability) from age 60 was estimated for those with and without EDS.

Results The study participants were on average 64 years old and 47% were men. Those with EDS were more likely to develop disability than those without (OR 1.48, 95%CI 1.04 - 2.09). The HR for mortality associated with having EDS was 1.36 (95% CI 1.02 – 1.82). The results from life table analysis suggest that a sixty-year-old individual with EDS lived three years less overall, and similarly three years less, free from disability, than his/her non-sleepy counterpart.

Conclusions EDS is associated with higher likelihood of disability, increased risk of mortality, and substantially shorter overall and disability-free life expectancy at age 60.

Keywords sleepiness, disability, mortality, life expectancy

Introduction

Excessive daytime sleepiness (EDS), the irresistible urge to fall asleep when one's intention is to remain awake, is a relatively common condition, affecting up to 30% of the general population.[1,2] EDS has been associated with chronic conditions, such as depression and diabetes, risk factors such as reduced physical activity, and consequences such as increased risk of accidents and injuries. [3-5] For these reasons, EDS may be associated with disability and mortality.

A recent longitudinal study in a Japanese population found an increased risk of incident disability with EDS.[6] Another study similarly found an association between EDS and incident disability, but EDS was measured in combination with other symptoms of sleep, as "dyssomnia".[7] The four large population studies that assessed the relationship between EDS and mortality have produced inconsistent results.[8-11] The latest study with the strongest study design (large sample size, appropriate control of confounders and measurement of EDS) suggests an increased risk of mortality with EDS, but its generalizability is limited by the low response rate (37%). To our knowledge, no studies have assessed the extent to which EDS may be a marker of burden of disease over the life course.

Through the Wisconsin Longitudinal Study, a life-course study on (mostly non-Hispanic, white) American high school graduates with self-reported measures of sleep health, disability and mortality data, this study aims to assess the likelihood of developing disability, the mortality risk, and the difference in life expectancy (with or without disability) associated with having (chronic) EDS.

METHODS

The Wisconsin Longitudinal Study

In 1957, a third of all graduates from the (public/ private/ parochial) high schools of Wisconsin, born between 1937 and 1940 were randomly sampled and recruited into the Wisconsin Longitudinal Study. This 10,317 (5326 women and 4991 men) high school graduates, who were mostly white and non-Hispanic, were followed-up over the years (1964, 1975, 1992, 2004 and 2011); in person, through mail, phone, or any combination of the aforementioned approaches. The primary focus of the Wisconsin Longitudinal Study was to assess the ways through which adolescent achievements and aspirations were formed, and their influence on further education and career. The focus of the study shifted as the population aged, to cover more relevant areas throughout the life-course such as health and well-being, family formation, occupational experience, retirement, and cause of death. Self-reported data on daytime sleepiness was first introduced in 2004. Information on disability was available in 2004 and 2011, and mortality up to (November) 2014. In 2004, the size of the Wisconsin Longitudinal Study was reduced to 7,732 (follow-up rate 86%, taking into account deaths). Detailed information on the characteristics of the study participants lost to follow up have been discussed in previous publications.[12]

Data from the graduates' siblings (since 1993), spouses (2004) and sibling spouses (2005) were also collected; but the current study focuses on the graduates only.

This study used the public release version of the Wisconsin Longitudinal Study dataset, available online at http://www.ssc.wisc.edu/wlsresearch/data.[13]

Exposures

The main exposure of this study was EDS, based on the question: "How often do you have extreme sleepiness in the daytime when you have to struggle against falling asleep?" Those who answered "never or rarely" or "sometimes" were classified into the 'Non-EDS' group; and those who answered "several times a week (3-

5)" or "every day or almost every day" were classified into the 'EDS' group. Whether EDS was chronic was assessed through the following question "Have you had this problem for a month or more?" As a majority (96%) of the participants answered 'yes', we did not further stratify the EDS group into chronic and non-chronic EDS.

Outcome measures

Disability was defined as requiring assistance from a family member or friend for personal care for a month or more, due to health condition, illness or disability; or individuals receiving disability benefits. The activities involved in "personal care" were bathing, dressing, eating, going to the bathroom, getting around inside the house or getting outside, shopping, cooking, housework or laundry, managing money, making phone calls and taking medications (similar to the components of "Instrumental activities of daily living" identified by Lawton & Brody[14]). These data were collected through phone interviews/ in person in the Wisconsin Longitudinal Study in the 2004 and 2011 data collection waves.

Data on mortality were collected from several sources: periodic linkage with the national health index and social security administration's death index, as well as through periodic study surveys of the participants' family members. The censor date was November 2014. In our analyses, we used all-cause, instead of cause-specific mortality data, due lack of power.

Covariates

The covariates to be adjusted in the analyses were identified through a directed acyclic graph (DAG, eFigure 2 in the Supplement)[15], built using DAGitty v.2.3.[16] The use of a DAG helps us identify the minimum set of covariates that need to be adjusted to remove exposure-outcome confounding, and at the same time, avoid creating selection bias that may result from inappropriate confounder adjustment. According to our DAG, we needed to adjust for the following covariates: age, sex, education, smoking status, alcohol drinking, body mass index, asthma, diabetes, mental health, and CVD status/history (hypertension, hypercholesterolemia, history of heart problems and stroke). All measures were available in the Wisconsin Longitudinal Study dataset, collected through self-reported questionnaires and/or phone surveys.

Statistical analysis

Baseline characteristics

The baseline levels of covariates in our final dataset were summarized; overall, as well as with stratification by baseline EDS status. The differences in baseline levels of covariates by EDS status were compared using simple linear regression for continuous covariates, and simple logistic regression for categorical covariates.

The relationship between EDS and mortality

The association between EDS and all-cause mortality was assessed with Cox proportional hazards regression models, with adjustment for sex, education, smoking, and alcohol drinking behaviour (model 1), and for body mass index, SF-12 mental component score, asthma, diabetes and cardiovascular disease/events (model 2). Age was used as the time-scale in the Cox models. We tested for interaction by sex.

The relationship between EDS and disability

The relationship between EDS and disability was assessed both cross-sectionally, and longitudinally (in those without baseline disability and returned to the study in 2011). In both analyses, multiple logistic regression was used, adjusting for sex, education, smoking, alcohol drinking behaviour (model 1), body mass index, SF-12 mental component score, asthma, diabetes and cardiovascular disease/events (model 2). We also tested for interaction by sex.

The expected life years with and without disability, in those with or without EDS

To calculate the life expectancy in men and women without EDS, we built abridged lifetables for age 60 to 85+ with 5-year intervals, using the age- and sex-specific mortality rates for white non-Hispanic Americans in 2004 reported by the Centers for Disease Control and Prevention. We assumed that the mortality rate in the general population was the same as the mortality rate in the population without EDS. To calculate the life expectancy in those with EDS, we built another set of abridged lifetables with mortality rates from the population without EDS multiplied by the hazard ratio of EDS for mortality from our Cox models. We assumed that the hazard ratio remained constant with age.

To apportion the derived expected life years to years lived with and without disability, we required information on the proportion of individuals with or without disability, in those with and without EDS, at each age interval. This information was not available through our dataset due to the narrow age range of our study participants when disability was measured (63 to 67 years old). Hence we obtained the age- and sex-specific proportion of individuals with and without EDS in American adults (with at least high school education) in 2004 through the Survey of Income and Program Participation in the US, and apportioned them by EDS status, using the following formulae:[17,18]

$$1-p * Ru + p*RR*Ru = R$$
$$RR = Re/Ru$$
$$RR = OR/ ((1-Ru) + Ru(OR))$$

Where p is the prevalence of EDS (obtained from our dataset, and assumed to be constant with age; Ru is the risk of disability in those without EDS; Re is the risk of disability in those with EDS; RR is the risk ratio between disability and EDS; R is the risk of disability for the whole population obtained from the Survey of Income and Program Participation; and OR is the cross-sectional odds ratio between disability and EDS estimated from our study, assumed to be constant with age.

The number of person years lived within an age interval (Lx) was multiplied by the proportion of individuals with and without disability to obtain the expected life years with and without disability, in population with or without EDS.

Sensitivity analysis

We tested the robustness of our findings on the difference in expected life years (with and without disability) between those with and without EDS, by repeating the calculations using the lower and upper bounds of the 95% confidence intervals of the following values: 1) HR between EDS and mortality 2) cross-sectional OR between EDS and disability, 3) prevalence of EDS, and 4) age-specific proportion of disability.

Ethics

This study was approved by the Monash University Human Research Ethics Committee (Project number 1273) and the Deakin University Human Research Ethics Committee (Project number 2016-393).

Results

Study population

The Wisconsin Longitudinal Study started with 10,317 participants in 1957. Of those who survived until the data collection wave in 2003-2005, 85.6% completed surveys through phone or mail, of whom 72.1%

(n=5,575) had complete measures of exposure, covariates and outcome for this study (**Figure 1**). The analyses were performed only in those without a history of cancer, n=4,980.

Baseline Characteristics

In 2003-5, the included study participants were on average 64.3 (SD 0.7) years old, 47.4% were men, and had a mean of 13.7 (SD 2.3) years of education. Those with EDS were more likely to drink alcohol, have obesity, hypertension, hypercholesterolemia, history of heart problems, history of stroke, diabetes, a worse SF-12 mental component score and snored frequently during sleep (**Table 1**).

The relationship between EDS and disability

At baseline, participants with (chronic) EDS were more likely to have disability compared to those without EDS. The odds ratio was 2.06 (95%CI 1.46 to 2.90) after adjusting for sex, education, alcohol drinking and smoking status; 1.49 (95%CI 1.03 to 2.16) after additionally adjusting for body mass index, asthma, diabetes, SF-12 mental component score, hypertension, hypercholesterolemia, history of heart problems and stroke (**Table 2**). Similarly, in those without baseline disability who returned to the study in 2011 (n=4,002), we found that baseline EDS increased the odds of incident EDS with minimum (OR 1.83, 95%CI 1.31 – 2.56) and full (OR 1.48, 95%CI 1.04 – 2.09) adjustment of potential confounders (**Table 2**). We did not find evidence for interaction by sex in any of the cross-sectional or longitudinal models (**Table 2**).

The risk of all-cause mortality associated with having EDS

Participants with (chronic) EDS had worse survival compared to those without EDS (**Figure 2**). The hazard ratio (HR) was 1.55 (95%CI 1.17 to 2.05) after adjusting for sex, education, alcohol drinking and smoking status; 1.36 (95%CI 1.02 to 1.82) with additional adjustment for body mass index, asthma, diabetes, SF-12 mental component score, hypertension, hypercholesterolemia, history of heart problems and stroke (**Table 3**). We did not find evidence for interaction by sex.

Life expectancy with and without excessive daytime sleepiness

A sixty year old man without EDS had a life expectancy of 21 years, 19 years of which was free from disability. For a sixty year old woman, overall life expectancy was 24 years, and disability-free life expectancy was 20 years. The difference in expected life years (total, without disability, and with disability) between those with and without EDS, along with their upper and lower limits obtained from sensitivity analyses, are shown in **Table 4**. The differences in expected life years were similar between men and women. Using the HR and OR from model 1, we found that those with EDS lived approximately 4 years less overall, with around 5 years less disability-free life years. There was minimal difference (0.6 – 0.7 year) in the number of years lived with disability between those with and without EDS (**Figure 3**). Using the HR and OR from the more fully adjusted model 2, we found that the difference in overall life expectancy for a sixty-year-old with and without EDS was reduced to 3 years, and for disability-free life expectancy, also to 3 years. The difference in the number of years lived with disability between those with and without EDS became even smaller (0.2 year). The findings of reduced overall life expectancy and reduced disability-free life years, in those with compared to those without EDS, were consistent throughout the sensitivity analyses. Differences in life years lived with disability remained minimal and fell to around the null (**Table 4** and eTable 1 in the Supplementary appendix).

Discussion

This study of 4,980 high school graduates from Wisconsin found that having chronic EDS at age 60 was associated with a higher likelihood of developing disability at 7 years follow-up and a higher risk of mortality

over 10 years. The difference in overall life expectancy and disability-free life expectancy between those with and without chronic EDS were both 3 years, less in those with EDS.

Previous studies assessing the relationship between EDS and disability were mostly cross-sectional,[6,7,9,19,20] all supporting the greater likelihood of disability in those with EDS. In a longitudinal study, Park et al[7] found that EDS, in combination with other symptoms of poor sleep (trouble with falling asleep, waking up, and feeling unrested), increased the risk of incident disability measured through instrumental activities of daily living (HR = 1.20). The magnitude of the relationship was somewhat lower than what we found (OR=1.48), perhaps due to the mixture of sleep conditions included, the older study population (mean age 75 years), or the different confounder adjustment set in their study. Only demographic variables were included in Park et al.'s core analysis model; the remaining relevant confounders were included separately, in separate models. Nakakubo et al.[6] also found an increased risk of disability (similarly defined through instrumental activities of daily living) in those with EDS, but at a magnitude that is more similar to our study (HR = 1.41), after adjustment for a similar set of potential confounders. Our study showed that the findings from Nakakubo et al.,[6] which was based on a Japanese study population, can also be reproduced in our study population of highly educated, middle-aged American adults, who were mostly white and non-Hispanic.

Four large population studies have assessed the relationship between EDS and mortality, one of which (Rockwood et al.[11]) did not find any association, but three (Hays et al.,[9] Newman et al.,[10] and Empana et al.[8]) found that EDS increases the risk of mortality. Rockwood et al. defined EDS as the "tendency to sleep all day" and the response was limited to binary yes/no.[11] This measurement of EDS may be less sensitive to the one used in our study, which had a wider range of possible responses and a definition of EDS that is closer to the current consensus, the irresistible urge to fall asleep when the intention is to remain awake.[1] Rockwood et al. [11] also did not adjust for potential confounders such as diabetes, alcohol drinking, or hypertension. These may perhaps explain the differences in our results. From the three studies that found increased risk of mortality with EDS, Newman et al. found that EDS only increases risk of mortality in women, but not in men. They used a binary measurement of EDS and adjusted for sleep symptoms in their multivariable model.[10] Hays et al. found a similar HR (1.30) to our study (1.36), but did not test for interaction with sex.[9] The study by Empana et al., which had definition of EDS and confounder adjustment set that were similar to our study, produced a similar HR for the relationship between EDS and total mortality (Empana et al., = 1.33 vs. this study=1.36), and similarly did not find a significant interaction by sex. The findings from Empana et al. might have limited generalizability due to the low response rate (37%); our study has further confirmed that the result is reproducible in a representative sample of highly-educated, non-Hispanic, white American population.[8] Other studies which used the presence/duration of napping as a marker of EDS have also shown increased risk of mortality with (more) napping, which is consistent with our findings.[21]

The pathways through which EDS, independent of its underlying medical conditions, may cause disability and mortality have not been formally studied. We hypothesised that it is likely to be due to reduced physical activity/exercise associated with EDS,[22] or in much rarer instances, motor-vehicle accidents and/or occupational injuries, which have also been previously associated with EDS.[3-5] EDS may also reflect sleep deprivation; which has been associated with mortality risk factors such as sympathetic tone activation, and increased levels of circulating catecholamines, inflammatory, and hemostatic factors.[8,23,24] This indicates that for those with EDS, it is not only important to treat the underlying cause of EDS, but also to manage the high risk of developing disability and of mortality, that we have identified here.

We further extended our study to assess the implications of the relationship between EDS and mortality on life expectancy, and estimated that the overall expected life years and years lived with disability in those with EDS at age 60 were both reduced by 3 years, compared to those without EDS. This quantification of life expectancy with or without disability, in a population with or without EDS, has not been previously done and may help us better comprehend the extent to which EDS is both an important health condition and a marker of burden of disease and disability over the life course, requiring comprehensive prevention and management strategy.

In this study daytime sleepiness was measured through a standardized questionnaire, not through a validated questionnaire such as the Epworth Sleepiness Scale, or objectively, such as through Multiple Sleep Latency Test. However, the concept and definition of EDS applied to the questionnaire in the current study is coherent with the current consensus. Further, the questionnaire allowed for multi-level responses (non-binary), and took into account the chronicity of EDS (a strength that is not common to other self-reported questionnaires). The Wisconsin Longitudinal Study contained mostly white, non-Hispanic Americans and all study participants graduated from high school. It was estimated that about 75% of Wisconsin youth in 1950s graduated high school. Consequently, our results may not be generalizable to the remaining strata of the general population. Considering the long follow-up duration, the Wisconsin Longitudinal Study had a good follow-up rate (85.6%, between 1957 and 2005), but only 72.1% of those who returned had complete data on exposure, outcome and covariates for this study. Those with incomplete data were more likely to be women with lower education. There is a possibility of selection bias in our study, i.e. it can be that our results are not applicable to women with lower education. There was no record of validation studies for the measurement of disability in this study. However, the components of disability measure in this study closely resemble the instrumental activities of daily living measure identified by Lawton and Brody.[14] Due to the narrow age range, we could not obtain age-specific prevalence of disability from our dataset and had to acquire this information from the Survey of Income and Program Participation, which employed similar definition of disability. The prevalence of disability between ages 63 and 67 identified through our dataset matched quite well with that estimated from the Survey of Income and Program Participation dataset.

Implications and future directions

Our study further supports the hypothesised causal relationship between EDS with future disability and mortality. Through the quantification of its potential impact on life expectancy, our study provides a readily comprehensible form of information to the extent to which EDS is an important health problem, to the general public and health practitioners alike. We recommend future studies to assess the pathways through which EDS may affect disability and mortality, independently of its underlying medical conditions; and test the reproducibility of our findings using validated measurements of EDS, such as the Epworth Sleepiness Scale.

Conclusion

EDS is associated with increased risk of mortality, higher likelihood of having disability, as well as 3 years shorter overall life expectancy and 3 years shorter disability-free life expectancy, at age 60. It is not only important to treat the underlying cause of EDS but also to manage EDS to avoid its associated burden of disease later in life.

Conflicts of Interest

The authors have nothing to disclose

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Table 1. Baseline characteristics of participants included in the current study

	All study participants	Without EDS	With EDS	p-value
	N= 4,980	N= 4,550	N= 430	
Demographics				
Mean age, years	64.3 (0.7)	64.3 (0.7)	64.3 (0.7)	0.3
Men, n (%)	2,359 (47.4)	2,149 (47.2)	210 (48.8)	0.5
Education, years	13.7 (2.3)	13.7 (2.3)	13.8 (2.4)	0.4
Health behaviour				
Smoking, n (%)				
Never	2,024 (40.6)	1,856 (40.8)	168 (39.1)	
Former	2,356 (47.3)	2,148 (47.2)	208 (48.4)	0.5
Current	600 (12.0)	546 (12.0)	54 (12.6)	
Alcohol drinking, n(%)	823 (16.5)	746 (16.4)	77 (17.9)	<0.001
Self-reported health conditions				
Body mass index, kg/m^2				
Normal weight	1,302 (26.1)	1,223 (26.9)	79 (18.4)	
Overweight	2,113 (42.4)	1,959 (43.1)	154 (35.8)	<0.001
Obese	1,565 (31.4)	1,368 (30.1)	197 (45.8)	
Hypertension, n (%)	2,311 (46.4)	2,081 (45.7)	230 (53.5)	0.002
Hypercholesterolemia, n (%)	2,316 (46.5)	2,078 (45.7)	238 (55.3)	<0.001
History of heart problems, n (%)	724 (14.5)	634 (13.9)	90 (20.9)	<0.001
History of stroke, n (%)	136 (2.7)	117 (2.6)	19 (4.4)	0.04
Asthma, n (%)	425 (8.5)	378 (8.3)	47 (10.9)	0.07
Diabetes, n (%)	573 (11.5)	501 (11.0)	72 (16.7)	<0.001
Short Form 12 mental component score, unit	55.5 (6.3)	55.8 (5.9)	52.1 (8.9)	<0.001
Snoring, n (%)				
Never or rarely	845 (17.7)	783 (17.9)	62 (15.3)	
Sometimes	2,258 (47.2)	2,133 (48.7)	125 (30.9)	
Several nights a week	759 (15.9)	688 (15.7)	71 (17.5)	<0.001
Every night or almost every night	922 (19.3)	775 (17.7)	147 (36.3)	

All continuous variables were presented as mean (standard deviation) and categorical variables, as n (%)

Abbreviation: EDS; Excessive daytime sleepiness

Table 2. The relationship between excessive daytime sleepiness and disability a) cross-sectionally at baseline and b) longitudinally among those without disability at baseline

a)	Model 1			Model 2		
	OR	95%CI	P_{int}	OR	95%CI	P_{int}
Total cohort	2.06	(1.46 to 2.90)		1.49	(1.03 to 2.16)	
Men	2.30	(1.31 to 4.06)	0.7	1.68	(0.92 to 3.07)	0.6
Women	1.93	(1.25 to 2.98)		1.37	(0.85 to 2.20)	

b)	Model 1			Model 2		
	OR	95%CI	P_{int}	OR	95%CI	P_{int}
Total cohort	1.83	(1.31 to 2.56)		1.48	(1.04 to 2.09)	
Men	1.74	(1.12 to 2.70)	0.7	1.43	(0.90 to 2.28)	0.8
Women	1.96	(1.17 to 3.27)		1.49	(0.87 to 2.58)	

Model 1 was adjusted for sex, education, smoking, and alcohol drinking

Model 2 was adjusted for sex, education, smoking, alcohol drinking, body mass index categories, asthma, diabetes, SF-12 mental component score, hypertension, hypercholesterolaemia, history of heart problems, and history of stroke

P_{int} indicates p value for exposure/sex interaction test.

Abbreviations: CI; Confidence interval; OR, Odds ratio

The analysis was in (b) was performed in those without disability at baseline and those who returned to the study in 2011 (n= 4,002)

Table 3. 10-year mortality risk associated with excessive daytime sleepiness in the Wisconsin Longitudinal Study participants

	Model 1			Model 2		
	HR	95%CI	P_{int}	HR	95%CI	P_{int}
Total cohort	1.55	(1.17 to 2.05)		1.36	(1.02 to 1.82)	
Men	1.43	(0.95 to 2.13)	0.5	1.27	(0.84 to 1.92)	0.6
Women	1.63	(1.10 to 2.43)		1.38	(0.91 to 2.09)	

Model 1 was adjusted for sex, education, smoking, and alcohol drinking

Model 2 was adjusted for sex, education, smoking, alcohol drinking, body mass index categories, asthma, diabetes, SF-12 mental component score, hypertension, hypercholesterolaemia, history of heart problems, and history of stroke

Model 2 was adjusted for education, smoking, alcohol drinking, body mass index categories, asthma, diabetes, SF-12 mental health component, hypertension, hypercholesterolemia, history of heart problems, history of stroke (for total cohort, as well as sex)

P_{int} indicates p value for exposure/sex interaction test.

Abbreviations: CI; Confidence interval; HR, Hazard Ratio

Table 4. Difference in total life expectancy, life expectancy without disability, and life expectancy with disability, in men and women with and without EDS at age 60

	Difference in expected life years between those with and without EDS at age 60					
	Model 1			Model 2		
	Total	Without disability	With disability	Total	Without disability	With disability
Men	-3.86 (-6.03 to -1.47)	-4.48 (-6.10 to -2.75)	0.61 (-0.07 to 1.40)	-2.78 (-5.13 to -0.19)	-2.99 (-4.51 to -1.17)	0.21 (-0.62 to 1.02)
Women	-4.00 (-6.23 to -1.53)	-4.69 (-6.45 to -3.14)	0.68 (-0.30 to 1.77)	-2.89 (-5.31 to -0.20)	-3.05 (-4.63 to -1.41)	0.17 (-0.84 to 1.31)

Life expectancy with or without disability was calculated using (EDS-mortality) HR and (EDS-disability) OR from Model 1 (adjusts for sex, education, smoking, and alcohol drinking) or Model 2 (adjusts for variables in model 1 as well as body mass index categories, asthma, diabetes, mental health indicator, hypertension, hypercholesterolemia, history of heart problems, and history of stroke).

The numbers in brackets are the lower and upper limits obtained from sensitivity analyses, by altering the values of (EDS-mortality) HR, (EDS-disability) OR, prevalence of EDS, and age-specific disability proportion. The full results to the sensitivity analyses are shown in eTable 1 in the Supplementary appendix.

Abbreviation: EDS, Excessive daytime sleepiness

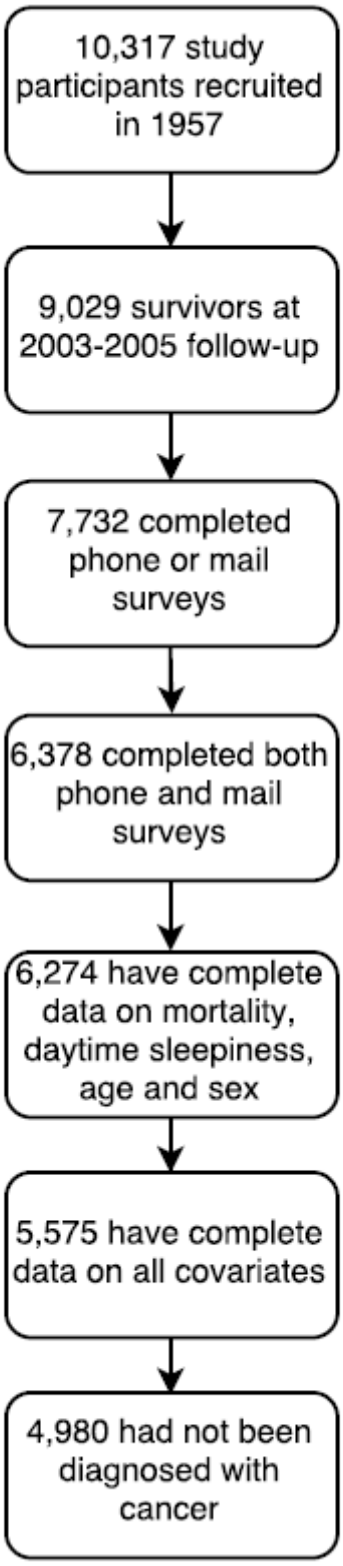

Figure 1. Flowchart

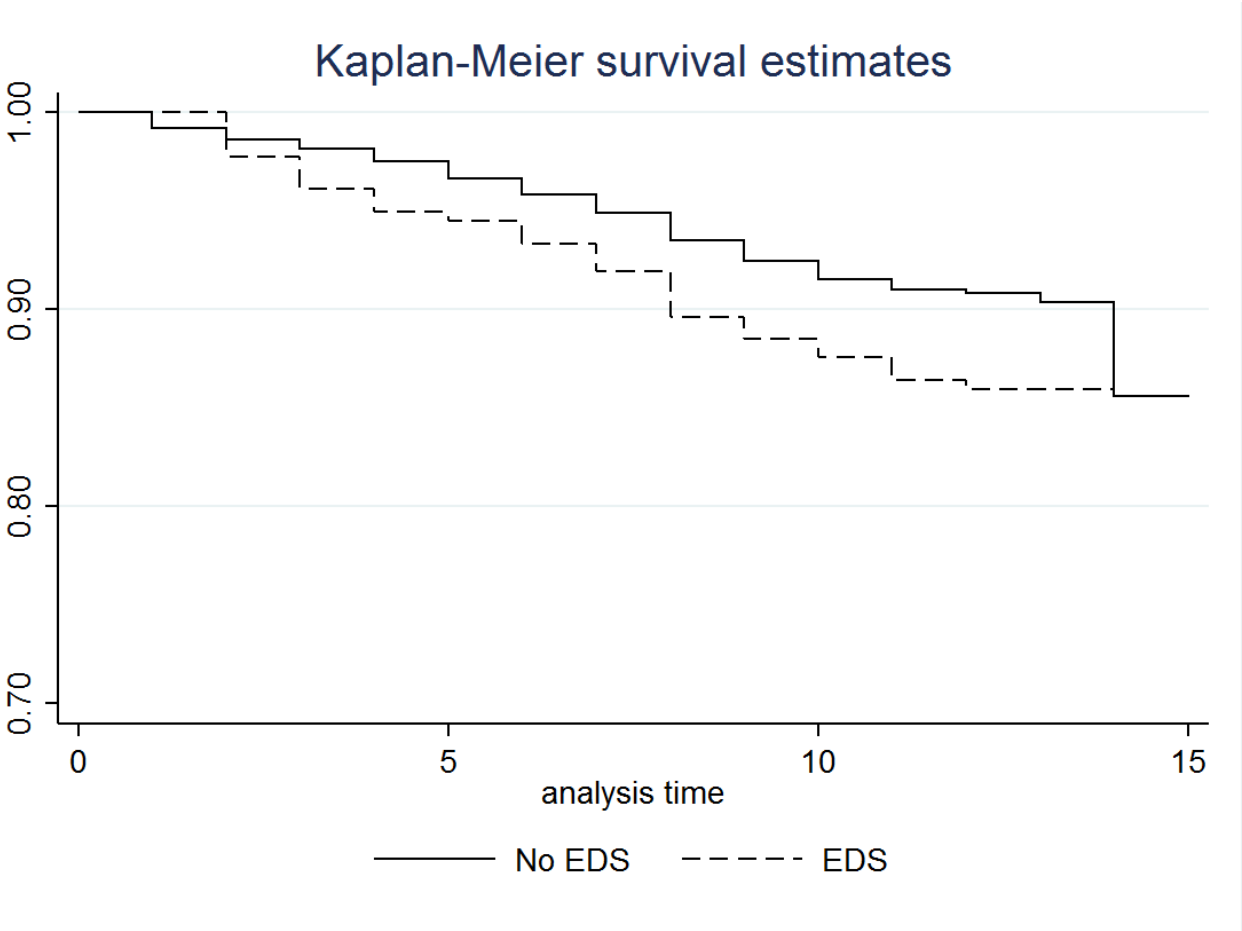

Figure 2. Survival curves by excessive daytime sleepiness status at baseline.

Abbreviation: EDS, Excessive daytime sleepiness

Supplementary appendix

Sleep health, mortality and life expectancy

Winda L. Ng, Jonathan E. Shaw, Anna Peeters

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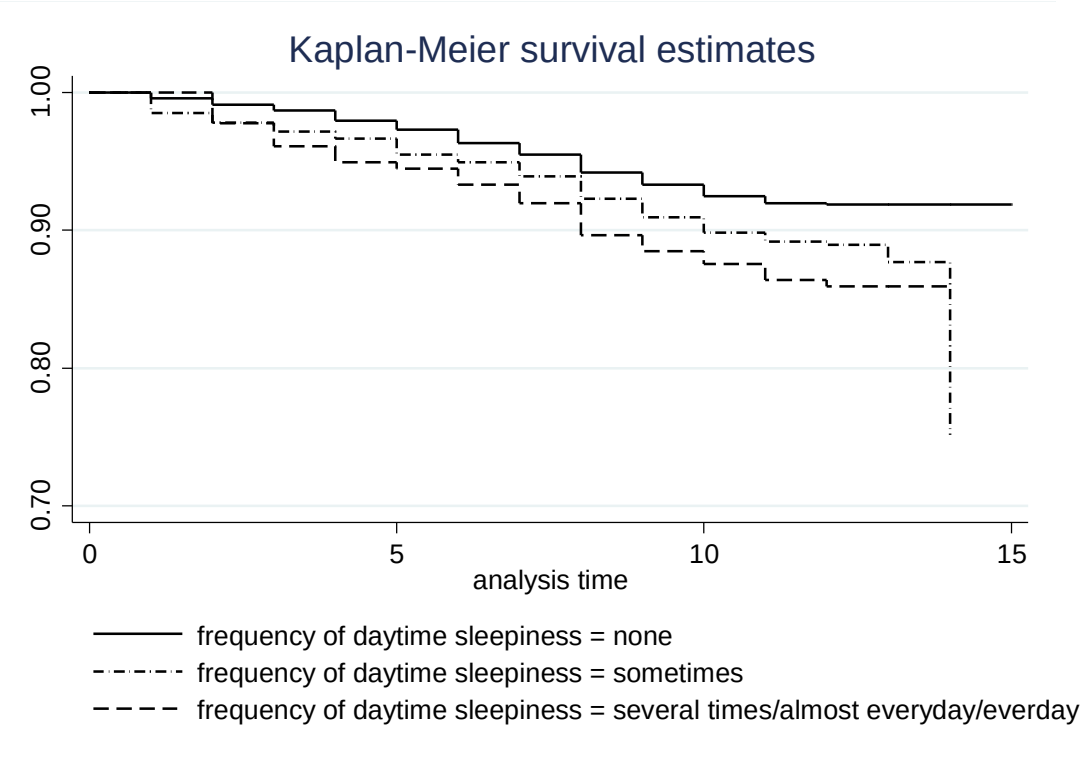
eTable 1. Full result to sensitivity analyses for expected life years with and without disability, in those with and without excessive daytime sleepiness

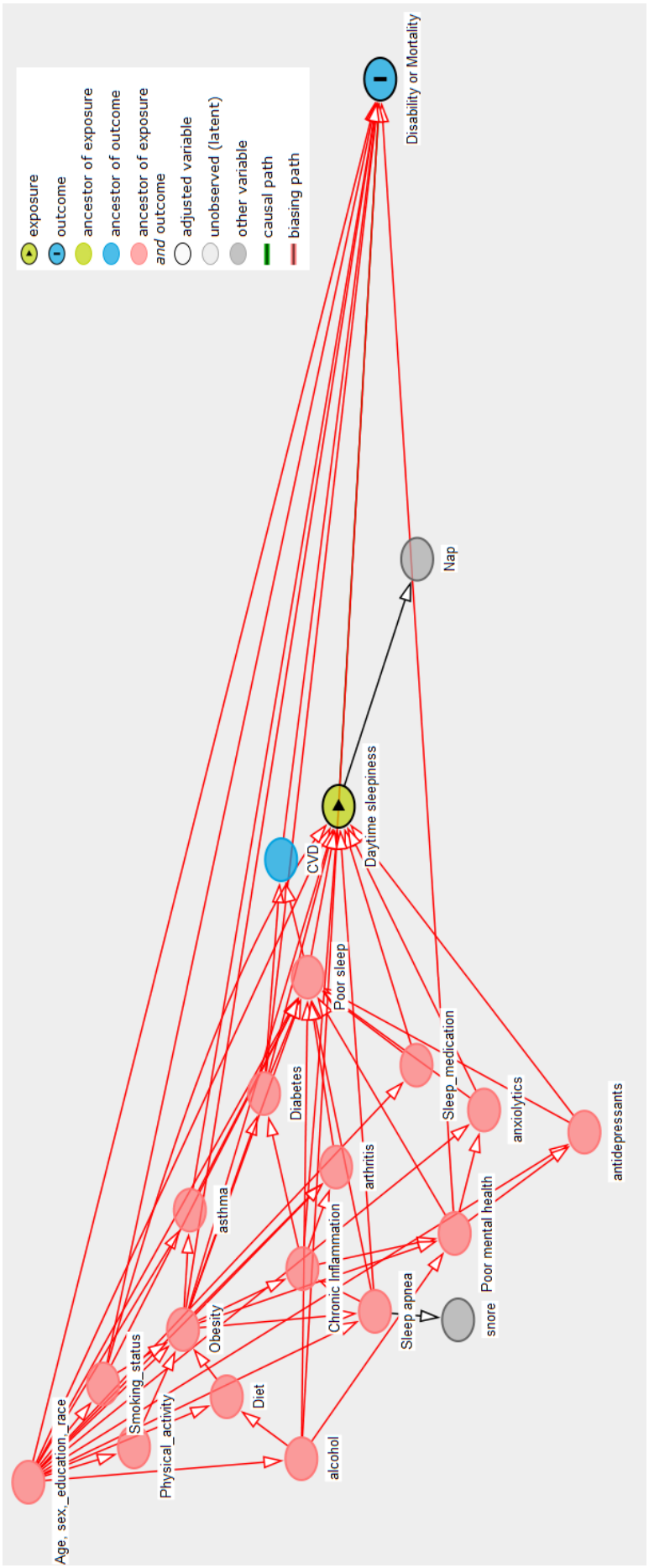
Changes to input variables	Difference in expected life years between those with and without EDS					
	Men			Women		
	Total	Without disability	With disability	Total	Without disability	With disability
Model 1						
Use lower CI of EDS-Disability OR	-3.86	-3.79	-0.07	-4.00	-3.71	-0.30
Use upper CI of EDS-Disability OR	-3.86	-5.27	1.40	-4.00	-5.78	1.77
Use lower CI of age-specific proportion of disability	-3.86	-4.41	0.55	-4.00	-4.65	0.64
Use upper CI of age-specific proportion of disability	-3.86	-4.54	0.67	-4.00	-4.73	0.72
Use lower CI of EDS prevalence	-3.86	-4.48	0.61	-4.00	-4.69	0.69
Use lower CI of EDS prevalence	-3.86	-4.47	0.61	-4.00	-4.68	0.68
Use lower CI of EDS-Mortality HR	-1.47	-2.75	1.28	-1.53	-3.14	1.61
Use lower CI of EDS-Mortality HR	-6.03	-6.10	0.07	-6.23	-6.45	0.22
Model 2						
Use lower CI of EDS-Disability OR	-2.78	-2.32	-0.46	-2.89	-2.05	-0.84
Use upper CI of EDS-Disability OR	-2.78	-3.80	1.02	-2.89	-4.20	1.31
Use lower CI of age-specific proportion of disability	-2.78	-2.98	0.20	-2.89	-3.06	0.17
Use upper CI of age-specific proportion of disability	-2.78	-3.00	0.22	-2.89	-3.05	0.16
Use lower CI of EDS prevalence	-2.78	-2.99	0.21	-2.89	-3.05	0.17
Use lower CI of EDS prevalence	-2.78	-2.99	0.21	-2.89	-3.05	0.17
Use lower CI of EDS-Mortality HR	-0.19	-1.17	0.98	-0.20	-1.41	1.21
Use lower CI of EDS-Mortality HR	-5.13	-4.51	-0.62	-5.31	-4.63	-0.67

Abbreviations: CI, Confidence interval; EDS, Excessive daytime sleepiness; HR, Hazard Ratio; OR, Odds ratio



eFigure 1. Survival curves by excessive daytime sleepiness status (no, sometimes, yes) at baseline

Abbreviation: EDS, Excessive daytime sleepiness



eFigure 2. Directed acyclic graph

Abbreviation: CVD, Cardiovascular disease

CHAPTER 9

Discussion and conclusion

9.1. Key findings

This thesis aimed to: (1) provide further understanding on the relationship between obesity and excessive daytime sleepiness (EDS), and the potential effect of weight loss interventions on daytime sleepiness, 2) assess the effect of weight loss interventions on use of hypnotics and sedatives, and 3) quantify the morbidity and mortality burden associated with having EDS. The extent to which this thesis has addressed the aforementioned aims is summarised below.

9.1.1. The relationship between obesity and excessive daytime sleepiness, and the potential effect of weight loss interventions on excessive daytime sleepiness

Through the study in Chapter 3, I found that being overweight or obese was associated with worse levels of daytime sleepiness (0.8 and 1.1 higher ESS scores respectively), and that being overweight was associated with 1.8 times higher likelihood of having EDS (defined through Epworth Sleepiness Scale score, ESS >10). This confirmed the cross-sectional relationship between obesity and EDS found by previous studies.[1-4]

However, due to several reasons, associations identified through cross-sectional studies cannot infer causation. Firstly, in cross-sectional studies, one is assuming that comparing the odds of having EDS in different individuals with and without obesity is the same as assessing the likelihood of acquiring EDS had the same people who were non-obese became obese. This is a strong assumption of "no between-person confounding". Secondly, temporal direction cannot be determined through cross-sectional studies, i.e. it is unclear whether obesity causes EDS, or vice versa.

Considering these limitations, I set out to perform another study assessing the relationship between obesity and EDS, this time with a prospective cohort study design (Chapter 4). To address the limitation of between-person confounding, I used weight change instead of baseline obesity status as our exposure variable. To address the problem with temporality, I could have chosen to assess incident EDS among those without EDS at baseline. However, from previous weight loss intervention studies, I hypothesised that a relatively large amount of weight change would be required to produce a small amount of change in daytime sleepiness measured through ESS (see subsection 2.3.1); if this were true, binary categorisation of daytime sleepiness would make it difficult to detect a weak relationship between weight change and daytime sleepiness. For these reasons, in Chapter 4, I assessed the relationship between weight change and daytime sleepiness as a continuous outcome.

The study results from Chapter 4 suggest that weight gain is associated with worse daytime sleepiness. The magnitude of association was relatively small (0.36 unit increase in ESS score per 10 kg weight gain) but consistent and robust throughout a series of sensitivity analyses. There was a significant interaction by sex, whereby the relationship between weight change and daytime sleepiness was only evident in women. This was unexpected, given previous findings of a stronger relationship between obesity and obstructive sleep apnea in men than in women,[5,6] and of the higher likelihood of men reporting higher ESS score than women.[6,7] It is unclear why we found no association between weight change and daytime sleepiness in men, but perhaps it is because in this study population, men were heavier at baseline with baseline weight negatively associated with degree of weight change. Another plausible explanation is the presence of other potential mediators such as obesity-related asthma, which only develops in women, but not in men.[8,9] No other studies have assessed the relationship between weight change and daytime sleepiness, stratified by sex.

Other longitudinal studies, have assessed the relationship between obesity and EDS.[8,10,11] They similarly found that baseline obesity or weight gain is associated with incident EDS; and weight loss, with EDS remittance. These studies have shown clear temporal direction between obesity and EDS. However, they had some limitations. Firstly, EDS was measured through an unvalidated questionnaire with one/two questions only. Secondly, whether causal inference can be drawn from their identified associations is unclear, because the extent to which the assumptions of (i) no unmeasured confounding, (ii) well-defined intervention (consistency), and (iii) positivity (non-zero chance of being treated) are fulfilled were not explicitly discussed in the texts.[12] Through the study in Chapter 4, I confirmed that weight gain is associated with worse daytime sleepiness, assessed through the ESS, a more widely used, validated tool to assess daytime sleepiness,[13,14] which has been shown to have good test-retest reliability.[15] I also presented a directed acyclic graph[16] to provide a transparent view to the rationale behind confounder selection and to show the extent to which I thought the assumption of "no unmeasured confounding" has been addressed in the analysis. I further described how the assumptions of "well-defined intervention" could affect the result, giving a clear picture of the conditions under which causal inference can be drawn from our study. The findings however, are still limited by the lack of a clear temporal direction between obesity and EDS.

A randomised controlled trial of weight loss interventions assessing daytime sleepiness as an outcome, provides a way to assess the causal relationship between obesity and EDS, with a clear temporal direction. Identifying causation from a randomised controlled trial is also more straightforward because random treatment allocation removes baseline exposure-outcome confounding, and "well-defined intervention" and "positivity" are inherent properties of intervention studies.[12] Therefore, we performed a systematic review and meta-analysis, looking at existing intervention studies (with or without a control group, randomised or non-randomised), assessing change in daytime sleepiness as an outcome (Chapter 5).

In Chapter 5, I found that daytime sleepiness improved following weight loss interventions in overweight or obese individuals, and to a greater degree in surgical than non-surgical weight loss interventions. There was no difference between the effect sizes obtained from controlled and uncontrolled studies. Further analysis suggests that there may be a dose-response relationship between the amount of weight loss, and the degree of improvement in daytime sleepiness. These findings further support my hypothesised causal effect of obesity on EDS, addressing the aforementioned limitations of Chapter 3 and 4.

The dose-response relationship between the amount of weight loss and the magnitude of change in daytime sleepiness that I found in Chapter 5 was non-linear (L-shaped), i.e. daytime sleepiness improves with more weight loss but after a certain point, further weight loss would not result in a greater improvement in daytime sleepiness (floor effect). This may explain why in the only randomised controlled trial comparing daytime sleepiness following weight loss through bariatric surgery and lifestyle modification, no difference in improvement of daytime sleepiness was found between the two treatment groups.[17] The floor effect is a common phenomenon in weight loss interventions assessing other outcomes.[18,19]

One may argue that perhaps it is not the weight loss per se that improved daytime sleepiness, but the method through which weight loss was achieved. For example, physical activity, a certain type of diet or a particular surgical prodecure may each have an effect on EDS that is independent of weight loss. This cannot be assessed in Chapter 5, because most of the weight loss interventions included in the review incorporated more than one type of weight loss interventions, although it is encouraging that a collective dose-reponse relationship between weight loss and improvement in daytime sleepiness was found across all included studies.

Through the systematic review in Chapter 5, I observed that weight loss interventions involving exercise/physical activity alone did not affect daytime sleepiness.[20-23] This may be due to the minimal amount of weight loss achieved (suggesting that physical activity/exercise in absence of weight change has no effect on daytime sleepiness), or due to lack of power. Using readily available data, in Chapter 6, I found that daytime sleepiness among those with baseline EDS improves following a workplace physical activity program, suggesting a potential unforeseen benefit of a workplace physical activity program on daytime sleepiness, although this needs to be confirmed by another study including a control group. Further analysis showed that the degree of improvement in daytime sleepiness was associated with the degree of reduction in BMI, supporting the findings in Chapter 3-5, regarding the relationship between obesity and EDS.

In addition to the total effect of obesity on EDS, this thesis also aimed to assess the pathways through which obesity may lead to EDS. The study in Chapter 4 quantified for the first time that approximately one-fifth of the relationship between weight change and daytime sleepiness was mediated through obstructive sleep apnea. This confirmed previous hypotheses on the occurence of obesity-related EDS, independent of obstructive sleep apnea (see subsection 2.3.1.1).[24] There was also evidence supporting the mediating effect of physical health, but not mental health or sleep duration, between weight change and daytime sleepiness. The role of more specific indicators of physical or mental health, such as depression, asthma, and diabetes, needs to be assessed.[8,24]

Taken together, through different study designs and methodologies, Part 1 of this thesis has shown consistent evidence supporting the relationship between obesity and EDS, and also a potential pathway through which obesity may lead to EDS. This strongly supports the hypothesis of a causal effect of obesity on EDS, and suggests that weight loss interventions may be considered as one of the treatment options for obese individuals with EDS.

9.1.2. The potential effect of weight loss interventions on use of hypnotics and sedatives

Encouraged by the findings of improved daytime sleepiness with weight loss; we commenced another study assessing the likely effect of gastric bypass surgery and intensive lifestyle modifications (low-/very-low calorie diet) on another sleep measure, use of hypnotics and sedatives (Chapter 7). Prior to the commencement of the study, I hypothesised that use of hypnotics and sedatives would similarly improve (reduce) following both weight loss interventions, potentially due to improvement in obesity-related sleep disorders. However, contrary to my hypothesis, I found that use of hypnotics and sedatives increased after gastric bypass, to a level that was 1.7 times, 2.0 times, and 2.2 times higher in the surgery than the intensive lifestyle group at 1-year, 2-years, and 3-years follow-up respectively. Similarly, among those who were hypnotics and sedatives users prior to the interventions, the average treatment dose (measured as defined daily doses (DDDs)) increased more following gastric bypass surgery than among those undergoing intensive lifestyle modification. Differences at 1-year, 2-years, and 3-years follow-up were 18 DDDs, 41 DDDs, and 57 DDDs respectively. A previous uncontrolled study in 165 Norwegian patients,[25] and a recently published Swedish study comparing 3,139 gastric bypass surgery patients to 31,390 non-obese general population controls,[26] also found increased use for hypnotics and sedatives following gastric bypass surgery. There was no exploration of the reasons for this observation.

Since there was no evidence for a dose-response relationship between the amount of weight loss and the degree of change in the use of hypnotics and sedatives in either of the treatment groups; perhaps it was not the weight loss, but the undertaking of gastric bypass procedure that is causing the increase in use of hypnotics and sedatives. The potential pathways through which the

undertaking of gastric bypass surgery may lead to increased use of hypnotics and sedatives is unknown, but there are some possible explanations, which I have outlined in Chapter 7. One of the hypotheses proposed was "addiction transfer".[27] Perhaps prior to gastric bypass surgery, patients consumed food as a source of comfort for their anxiety or depression; but following surgery, due to physiological changes, they were no longer able to consume as much food. Hence, they might choose to transfer their addictive behaviour to other substances, in this case hypnotics and sedatives. Previous studies have shown similar increases in substances such as recreational drugs and alcohol following gastric bypass surgery.[28-31] Another hypothesis was that, perhaps following the resolution/improvement in obstructive sleep apnea after gastric bypass, clinicians feel more comfortable in prescribing hypnotics and sedatives to patients. However, we found that the use of hypnotics and sedatives increased after gastric bypass surgery regardless of baseline use of continuous positive airway pressure (treatment for obstructive sleep apnea). Also, at baseline, there was no difference in the proportion who use sleep medications in those who were or were not using continuous positive airway pressure. A previous study, also using the Scandinavian Obesity Surgery Registry data, showed that use of continuous positive airway pressure decreased after gastric bypass surgery, potentially indicating resolution of obstructive sleep apnea.[32] Given the well-established link between the gastrointestinal tract and the brain,[33] it is also possible that gastric bypass surgery adversely affects brain-gut signalling, leading to disturbed sleep, or the actual or perceived need for hypnotics.

In the systematic review and meta-analysis in Chapter 5, I found a significant improvement in daytime sleepiness following surgical weight loss interventions, and yet in Chapter 7, I found an increased use of hypnotics and sedatives following gastric bypass surgery. At first glance, this may appear somewhat counterintuitive. Daytime sleepiness is the most common side effect from use of hypnotics and sedatives (due to incomplete clearance of the drugs),[34] and therefore it seems unlikely that gastric bypass surgery would lead to both increased use of hypnotics and sedatives and decreased level of daytime sleepiness. One can argue that the meta-analysis of surgical studies in Chapter 5 included a wide range of different surgical procedures (sleeve gastrectomy, gastric bypass, and gastric banding), which might have affected sleep health differently. However, in the two included prospective cohort studies in America and China that involved only gastric bypass surgeries, daytime sleepiness largely improved.[35,36] One possible explanation is that perhaps the improvement in sleep deprivation from consuming hypnotics and sedatives, far outweighs the side effect of daytime sleepiness produced by the hypnotics and sedatives. Alternatively, maybe the phenomenon of increased use of hypnotics and sedatives after gastric bypass surgery is only observed within the Swedish population, and not in the American or Chinese populations, due to the difference in the attitude towards hypnotics and sedatives prescriptions. In other words, if I were to assess the change in daytime sleepiness following gastric bypass surgery in a Swedish population, perhaps daytime sleepiness would have worsened. One other potential explanation is that perhaps sleep (daytime sleepiness) is improved in a majority of gastric bypass patients, and it is only in a minority of high-risk individuals that the use of hypnotics and sedatives increased. This would account for both the overall improvement in daytime sleepiness found in the review in Chapter 5, and the increase in use of hypnotics and sedatives found in the study in Chapter 7. Future studies need to assess daytime sleepiness, use of hypnotics and sedatives, and other sleep measures concurrently, following gastric bypass or any other types of bariatric surgery.

Regardless of the potential pathways, this novel finding on increased use of hypnotics and sedatives after gastric bypass surgery in Part 2 of the thesis, warrants a monitoring strategy for gastric bypass surgery patients. It is also important to assess if similar phenomenon can be observed following other types of bariatric or non-bariatric surgery.

9.1.3. The relationship between excessive daytime sleepiness, mortality, and life expectancy

In Chapter 8, we found that EDS increases the likelihood of developing disability at 7 years follow-up, with (OR = 1.48) and without (OR = 1.83) full adjustment of a range of relevant underlying medical conditions. There was no significant interaction by sex. This is consistent with findings from a previous longitudinal study by Nakakubo et al. (HR = 1.41) in a Japanese population.[37] I also found that EDS increases the risk of 10-year mortality, with (HR = 1.36) and without (HR = 1.55) full adjustment of potential confounders. There was no significant interaction by sex. This is consistent with findings from a previous study by Empana et al. with robust study design but low response rate (37%).[38] My study helped confirm that the results from Nakakubo et al and Empana et al are reproducible in a representative study sample of white, non-hispanic, highly educated Americans.

I also showed (for the first time) that EDS, as a marker of a range of medical conditions, was associated with 4 years reduction in life expectancy overall, and 5 years reduction of disability-free life expectancy. Further, independent of underlying medical conditions, EDS was associated with 3 years reduction in life expectancy overall as well as free from disability. There was little difference by sex. The expected life years lived with disability was similar in those with and without EDS (difference <1 years in both partially- and fully-adjusted models), and not robust to sensitivity analysis. These findings may provide a better understanding of the extent to which sleep problems are an important health risk to the general public.

In summary, Part 3 of this thesis has shown that chronic EDS is associated with increased likelihood of developing disability, increased risk of mortality, and reduced overall as well as disability-free life expectancy. This indicates that it is not only important to treat the underlying cause of EDS but also to manage its associated high risk of morbidity and mortality. It is uncertain how EDS, independent of its underlying medical conditions, causes disability or increases the risk of mortality. However, I hypothesise that it may occur through reduced physical activity/exercise[39] or more rarely through accidents and injuries.[40,41] It is also likely that individuals with EDS were sleep deprived. Sleep deprivation has been linked to sympathetic tone activation and higher levels of circulating catecholamines, inflammatory and hemostatic factors, all of which may influence mortality.[38,42,43]

9.1.4. Other findings

In addition to the main findings above, in Chapter 3, I also found that approximately one in six Australian workers has EDS. This suggests that EDS is not only common in high risk working population such as truck divers and shift-workers, but also in a general setting. EDS at workplaces needs to be reported, monitored and managed , to avoid injuries,[44] accidents,[41,45] and impaired work performance,[46,47] previously associated with EDS. Some institutions such as Google, Nike, Zappos, and Ben & Jerry's have adopted policies in support of napping at work, and have provided napping facilities for their employees to minimise loss of productivity due to EDS.[48]

Chapter 3 also showed that EDS appear to share a range of risk factors with obesity and non-communicable diseases, such as younger/older age, poor diet and poor mental health status. Perhaps EDS can be included as one of the health factors in an existing, broader management and preventive strategy for obesity and non-communicable diseases.

9.2. Limitations

A majority of the studies in this thesis relied on the Epworth Sleepiness Scale to assess daytime sleepiness. As with all self-reported measures, the accuracy of subjective reporting of daytime sleepiness may depend on the responder's mood, education, and perspectives. However, the Epworth Sleepiness Scale has been previously validated,[13,14] has been shown to have good test-retest reliability,[15] and more importantly, aims to assess daytime sleepiness across a wide range of settings.[49] Other subjective tools such as the Karolinska or the Stanford Sleepiness scale, and objective tools such as the Multiple Sleep Latency test and the Maintenance of Wakefulness Test, measure daytime sleepiness in one particular condition, and at one particular moment/in one particular day.[49,50] The Epworth Sleepiness Scale, despite its limitations, is the most feasible, widely available measure of daytime sleepiness, relevant to our study purposes.

The Sleep Heart Health Study dataset in Chapter 3 suffers from a high rate of missing data (53%), which might have introduced selection bias to our study analysis. This may not affect our main conclusion on the overall relationship between obesity and EDS, because the total relationship between obesity and EDS appears consistent through multiple studies with different methodologies and datasets (Part 1 of the thesis). However, this limitation of the study dataset may affect the conclusion on the potential mediating pathways between obesity and EDS, which was only assessed through the study in Chapter 4, using the Sleep Heart Health Study dataset. Although the results from sensitivity analyses in Chapter 4 were robust, future studies need to test the reproducibility of the findings using a dataset with higher follow-up rate, and to explore other potential mediating pathways between obesity and EDS. At the commencement of this thesis, to my knowledge, the Sleep Heart Health Study was the best available prospective cohort study which contains measurements of daytime sleepiness, weight, obstructive sleep apnea, and other relevant covariates at multiple timepoints.

Through the studies in this thesis, I could not distinguish whether the observed effect of obesity on EDS was due to obesity per se, or if it was due to the underlying causes of obesity, e.g. poor diet and physical activity. If the Sleep Heart Health Study dataset had measured more variables such as diet and physical activity, and at more time-points, in Chapter 4, I could have performed a similar study to Danaei et al,[51] using g-formula or other time-varying analysis method to assess the effect of different hypothetical lifestyle interventions (e.g. exercising ≥30 minutes/day, drinking 1 less soft drink serving a week, eating less than 3 servings of red meat/week, etc),[51] instead of overall weight change, on daytime sleepiness. In the review in Chapter 5, I could not perform a stratified analysis by types of weight loss interventions because most studies involved more than one strategy for weight loss. However, it is encouraging to note that I found a general improvement in daytime sleepiness across different types of weight loss interventions, and a collective dose response between their amount of weight loss and the degree in improvement in the level of daytime sleepiness.

The conclusion of increased use of hypnotics and sedatives following gastric bypass surgery was determined only through the Swedish registry data. I cannot comment on the reproducibility of this finding in other countries, e.g. Australia and U.S., which may have different regulations or perceptions towards prescribing hypnotics and sedatives. I am also unable to generalise the findings to other types of bariatric surgery, or to other closely relevant drugs such as, antidepressants and anxiolytics.

Other limitations specific to each study are described within each chapter.

9.3. Strengths

This thesis utilised a variety of different methodologies and datasets to assess the relationship between obesity and EDS, and consistently showed a relationship between obesity/weight gain with worse daytime sleepiness; and weight loss, with better daytime sleepiness. The studies collectively provide robust evidence supporting the relationship between obesity and EDS. Of the nine Bradford Hill criteria of causation, the studies in this thesis tick the boxes for temporal relationship, dose-relationship, consistency, plausibility (through mediation analysis), and experiment.

In Chapter 4, I confirmed for the first time, the hypothesis that obstructive sleep apnea and poor overall physical health may mediate the relationship between weight change and daytime sleepiness, through a mediation analysis. I used a relatively new methodology outlined by VanderWeele et al, which allows for exposure-mediator interaction, and through a causal framework, outlined the conditions under which our identified mediation may be causal.[52]

The study on use of hypnotics and sedatives in Swedish obese adults who undertook gastric bypass surgery and intensive lifestyle modification in Chapter 7, utilised nation-wide data from multiple Swedish registries. This offers the advantage of a large sample size, low rate of loss to follow-up and study findings generalizable to Sweden and perhaps other Nordic or European countries more broadly.

The study in Chapter 8 was the first to assess the implication of EDS-related disability and mortality on life expectancy, providing a readily comprehensible form of information to the general public on the extent to which EDS is an important health condition.

Other strengths specific to each study are described within each chapter.

9.4. Implications

This thesis adds to the further understanding of the relationship between obesity and EDS, providing a more comprehensive view of the consequences of obesity on our health. The study findings also contribute to the development of a better management strategy for obesity. For example, given the relationship between obesity and EDS, clinicians can now be advised to screen for EDS in obese patients, regardless of the presence of obstructive sleep apnea, and inform patients of the consequences of EDS, such as injuries,[44] accidents,[41,45] and reduced professional performance,[46,47,53] which may provide them with further motivation to lose weight.

EDS is the most commonly received complaint in sleep clinics;[54] therefore, a well-developed diagnosis and treatment strategy for EDS is required. This thesis adds to the rationale for including obesity as one of the potential causes of EDS, separate to obstructive sleep apnea,and supports the recommendation of weight loss as an alternative treatment option for EDS, when other alternatives such as continuous positive airway pressure are not suitable.

The finding of improved daytime sleepiness following weight loss interventions in overweight or obese individuals adds to the incentives of joining or performing or weight loss interventions, which can be advertised to relevant individuals or institutions. Similarly, the finding of immediate and sustained improvement in daytime sleepiness following workplace physical activity interventions in those at higher risk, may also further motivate the adoption of a healthy lifestyle, with or without the intention to lose weight.

Given the rising prevalence of severe obesity,[55] there is a growing need for bariatric surgery and the understanding of its potential effects on health and quality of life. The finding of increased use of hypnotics and sedatives following gastric bypass surgery in this thesis contributes to the further

understanding of the potential side effects of bariatric surgery, which may influence the inclusion/exlusion criteria for recommending bariatric surgery, the selection of the type of bariatric surgery, and the post-surgical management strategy for patients who undertake gastric bypass surgery.

The findings on the relationship between obesity and EDS, and the morbidity and mortality burden associated with having EDS, may provide a greater understanding of the importance of obesity-related sleep problems, and give a clearer picture to the general public, regarding the extent to which sleep is an important area of health that cannot be ignored. Perhaps this thesis may also trigger more research into obesity-related sleep problems, an area that has been underrecognised in obesity research.

9.5. Directions for future studies

Future research assessing the relationship between obesity and EDS may attempt to reproduce our finding on the mediating effect of obstructive sleep apnea and explore the potential mediating role of more specific physical/mental health indicators in this relationship. Studies may also try to distinguish the effect of obesity per se, from its causes such as diet and physical activity, on EDS. This could be achieved through a randomised controlled trial comparing different types of lifestyle interventions aiming for weight loss; or more practically, by comparing the effect of hypothetical lifestyle inteventions aiming for weight loss,[51] through a prospective cohort study.

Given the finding of increased use of hypnotics and sedatives after gastric bypass surgery, it is important that future studies assess whether similar phenomenon are observed following other types of (bariatric and non-bariatric) surgery; and the potential pathways through which gastric bypass surgery may lead to increased use of hypnotics and sedatives. Further understanding in this area may help prevent the increase in prescription of hypnotics and sedatives, which is known to have unfavourable side effects.[34,56] If sleep health truly is disturbed after surgery, other non-pharmacological means such as the cognitive behavioural therapy for insomnia, could be offered instead of hypnotics and sedatives. If it is not sleep that worsened following gastric bypass surgery, but the increased intake of hypnotics and sedatives was merely a result of “addiction transfer”,[27] then the presence of addiction must be screened for, and a counterstrategy proposed, immediately following gastric bypass surgery. Further, if the addiction theory was true, perhaps gastric bypass surgery should not be recommended to high-risk individuals at baseline.

I also recommend future research to assess the effect of gastric bypass surgery (with or without other types of surgeries) on daytime sleepiness, the use of hypnotics and sedatives, and other measures of sleep concurrently. This is to understand whether and why daytime sleepiness and hypnotics and sedatives, respond differently to gastric bypass surgery. Other closely relevant measures such as use of anxiolytics and antidepressants, and other mental health measures may also be included, to give a greater overall picture of quality of life following gastric bypass surgery.

Conclusion

This thesis has shown strong evidence supporting the causal effect of obesity on excessive daytime sleepiness and clarified the potential benefit of weight loss on daytime sleepiness. The finding of increased use of sleep medications after gastric bypass surgery was unexpected, and requires further investigation. The quantification of the expected life years lost associated with having excessive daytime sleepiness, provides insights to the extent to which sleep problems are an important health factor in the society. Taken together, the findings from this thesis provides a substantial advancement in our understanding of the health consequences of obesity, and may contribute to the development of an improved management strategies for obesity and sleep problems. From the perspective of sleep health, the findings from this thesis may help improve the diagnostic and treatment strategy for excessive daytime sleepiness, the most commonly received complaint in sleep clinics.

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APPENDIX: List of publications, presentations, awards, and professional roles

Publications by the candidate relevant to the thesis

1. **Liviya Ng W**, Freak-Poli R, Peeters A**.** The prevalence and characteristics associated with excessive daytime sleepiness among Australian workers. J Occup Environ Med. 2014;56(9):935-45.

2. **Ng WL,** Freak-Poli R, Stevenson C, Peeters A**.** The Immediate and Sustained long-Term Changes in Daytime Sleepiness After Participation in a Workplace Pedometer Program: A Prospective Cohort Study. J Occup Environ Med. 2015;57(8):873-81.

3. **Ng WL**, Stevenson C, Wong E, Tanamas S, Boelsen-Robinson T, Shaw J, Naughton M, Dixon J, Peeters A. Does intentional weight-loss improve daytime sleepiness? – A systematic review and meta-analysis. Obesity reviews. 2017 Apr;18(4):460-75.

Additional peer-reviewed publications

1. Tanamas SK, Permatahati V, **Ng WL**, Backholer K, Wolfe R, Shaw JE, et al. Estimating the proportion of metabolic health outcomes attributable to obesity: a cross-sectional exploration of body mass index and waist circumference combinations. *BMC Obes*. 2015;3:4

2. Tanamas SK, **Ng WL**, Backholer K, Hodge A, Zimmet PZ, Peeters A**.** Quantifying the proportion of deaths due to body mass index- and waist circumference-defined obesity. Obesity (Silver Spring). 2016;24(3):735-42.

3. Bihan H, **Ng WL**, Magliano DJ, Shaw JE. Predictors of efficacy of GLP-1 agonists and DPP-4 inhibitors: A systematic review. Diabetes Res Clin Pract. 2016 Nov;121:27-34.

4. Chimeddamba O, Gearon E, Stevenson C, **Liviya Ng W**, Baasai B, Peeters A. Trends in adult overweight and obesity prevalence in Mongolia, 2005-2013. Obesity (Silver Spring). 2016 Oct;24(10):2194-201.

Conference presentations

**Published abstracts*

- **Ng WL**, Peeters A, Näslund I, Ottosson J, Johansson K, Marcus C, Shaw J, Bruze G, Sundström J, Neovius M. Change in use of sleep medications after gastric bypasss surgery or intensive lifestyle treatment in obese adults. Victorian Obesity Consortium, Melbourne, December 2016 – **oral presentation**

- **Ng WL**, Peeters A, Näslund I, Ottosson J, Johansson K, Marcus C, Shaw J, Bruze G, Sundström J, Neovius M. Change in use of sleep medications after gastric bypasss surgery or intensive lifestyle treatment in obese adults. Rod Andrew award competition, Melbourne, November 2016 – **oral presentation**

- ***Ng WL**, Stevenson C, Wong E, Tanamas S, Boelsen-Robinson T, Shaw J, Naughton M, Dixon J, Peeters A. Does intentional weight loss improve excessive daytime sleepiness? – A systematic review

and meta-analysis. International Congress on Obesity 2016, Vancouver, May 2016 – **oral presentation**

- ***Ng WL**, Stevenson C, Wong E, Tanamas S, Boelsen-Robinson T, Shaw J, Naughton M, Dixon J, Peeters A. Does intentional weight loss improve excessive daytime sleepiness? – A systematic review and meta-analysis protocol. Sleep Down Under 2015, Melbourne, October 2015 – **poster presentation**

- **Ng WL,** Freak-Poli R, Peeters A. The association between participation in a workplace pedometer program and a long-term change in the level of daytime sleepiness. Victorian Obesity Consortium Evening Symposium, Melbourne, November 2014 **– oral presentation**

- **Ng WL**, Freak-Poli R, Peeters A. Evaluation of the change in the level of daytime sleepiness after participation in a pedometer-based workplace health program. Alfred Week Research Poster Display, Melbourne, October 2014 – **poster presentation, awarded the Senior Medical Staff Prize for Clinical/Public Health Research 2014.**

- ***Ng WL**, Freak-Poli R, Peeters A. The association between obesity and excessive daytime sleepiness in Australian workers. Australian & New Zealand Obesity Society Annual Scientific Meeting, Sydney, October 2014 – **poster presentation**

- ***Ng WL,** Freak-Poli R, Peeters A. The prevalence and characteristics associated with excessive daytime sleepiness among Australian workers. 7th Asian-Oceania Conference of Obesity, Bandung, October 2013 – **oral presentation**

- **Ng WL,** Freak-Poli R, Peeters A. The association between participation in a workplace pedometer program and a long-term change in the level of daytime sleepiness. AMREP ECR conference, Melbourne, September 2014 – **oral presentation**

- ***Ng WL,** Freak-Poli R, Peeters A. The association between participation in a workplace pedometer program and a long-term change in the level of daytime sleepiness. 12th International Congress on Obesity, Kuala Lumpur, March 2014 – **oral presentation, selected for press release, and nominated as one of the seven highlights of the day**

- ***Ng WL**, Freak-Poli R, Peeters A. Evaluation of the change in the level of daytime sleepiness after participation in a pedometer-based workplace health program. Australian & New Zealand Obesity Society Annual Scientific Meeting, Melbourne, October 2013 – **poster presentation**

Awards, Prizes, and Scholarships

- The Harold Mitchell Travelling Fellowship, 2016
- The Monash Postgraduate Travel Grant Award, 2016
- The Senior Medical Staff Prize for Clinical/Public Health Research, 2014
- The Baker IDI Travel Grant Award, 2014
- The Baker IDI Bright-Sparks Scholarship Top Up, 2014
- The Monash International Postgraduate Research Scholarship, 2014

- The Faculty of Medicine International Postgraduate Research Scholarship, 2013
- The Monash Graduate Scholarship, 2013

Professional roles

- Invited speaker at Umeå University, Umeå, Sweden, on the topic of "Obesity and Sleep", 2016
- Guest journal peer-reviewer, *Prevention Science*, 2016
- Guest journal peer-reviewer, *Sleep and Biological Rhythm*, 2016
- Guest journal peer-reviewer, *Journal of the ASEAN Federation of Endocrine Societies*, 2016
- Initiator and current director of Methods club (Regular meetings amongst epidemiologists to share experience in utilising various research methodologies) at Deakin University, 2015-current
- Guest journal peer-reviewer, Diabetes Research and Clinical Practise, 2016
- Invited speaker for B.MedSc(Hons) international students orientation week, 2015
- Examiner for B.MedSci(Hons) mid year departmental oral presentation, at School of Public Health and Preventive Medicine, Monash University, 2015
- Guest journal peer-reviewer, *BMJ*, 2015
- Guest journal peer-reviewer, *BMC Endocrine Disorders*, 2015-2016
- Tutor for Introduction to Biostatistics at School of Public Health and Preventive Medicine, Monash University, 2015
- Tutor for Introduction to Epidemiology and Biostatistics (MPH5020) at School of Public Health and Preventive Medicine, Monash University, 2014-2015

Media

- The published article "Does intentional weight-loss improve daytime sleepiness? – A systematic review and meta-analysis" is covered or referenced by the following media agencies:
    - *The Australian* (http://www.theaustralian.com.au/life/health-wellbeing/sleep-a-factor-in-obesity-alzheimers-cognitive-function/news-story/4bd4d16fed2e5edd8d64f43367aa7745)
    - *Endocrine Today*/healio.com (http://www.healio.com/endocrinology/obesity/news/in-the-journals/%7B3653a6ee-baeb-4db0-9b62-0f5b4ccb71a3%7D/intentional-weight-loss-decreases-daytime-sleepiness)
    - *9coach* (http://coach.nine.com.au/2017/02/06/15/51/daytime-sleepiness)

- *The Healthy Mummy* (*https://www.healthymummy.com/study-finds-weight-loss-helps-with-daytime-sleepiness/*)
- *Tempo, Metronews, Australia plus Indonesia* (article in Indonesian) (*https://www.tempo.co/read/abc/2017/02/07/20170207075721/penurunan-berat-badan-bisa-mengurangi-kantuk-berlebihan*)
- *HealthyDay News*, which distributed it to *Neurology Advisor, Physician's weekly, Medical Express and Pyschiatry Advisor*
- *National Radio News*

- The conference presentation on "The association between participation in a workplace pedometer program and a long-term change in the level of daytime sleepiness " at the 12th International Congress on Obesity, Kuala Lumpur, March 2014, was selected for press release. Available from: http://www.worldobesity.org/site_media/uploads/ICO2014_Media_Alert_Day_2_website.pdf

Errata & Addendum

Additions are underlined and deletions are struck through

Chapter 2, page 8, paragraph 1: "…intake from increased opportunity to eat and hunger (associated with lower leptin and higher ghrelin) and/or through reduced energy expenditure rom altered thermoregulation and increased fatigue (**Figure 1**).[20,21] Some small scale experimental studies (n≤23) have shown that sleep deprivation may also cause craving for calorie-dense food,[197-200] suggesting another potential pathway between short sleep duration and obesity. However, results from observational cross-sectional studies have consistently confirmed this, some showing higher fat but lower carbohydrate consumption among short-sleepers[201-202] (which is contrary to the experimental study showing higher carbohydrate consumption[197]), and some showing no difference in fat and carbohydrate consumption with categories of sleep duration.[203-204] In comparison, the finding of higher sugar and caffeine intake from beverages among short sleepers were more consistent.[203-204]"

Chapter 2, page 18, paragraph 2: "Sleep-related breathing disoders include obstructive sleep apnea, central sleep apnea, and sleep-related hypoventilation/hypoxemia syndrome.[61] Obstructive sleep apnea, often encountered in individuals with obesity,[64] refers to the cessation or difficulty of breathing during sleep, due to obstructions of the upper airway, often accompanied by heavy snoring.[61] To be diagnosed with sleep apnea, there must be a total of more than 15 events (per hour) of apnea (complete cessation of breathing) or hypopnea (reduced breathing due to partial obstruction of airway), or arousal (due to increased respiratory efforts) measured through an overnight polysomnography test. Diagnosis of sleep apnea can also be established when there are 5 or more events per hour, and at least one of the following signs or symptoms: snoring, observed breathing pauses, excessive daytime sleepiness, and insomnia.[61] The scoring of apnea and hypopnea events, follows the guideline provided by the American Academy of Sleep Medicine,[55] which has changed throughout the years. [205,206] Sleep laboratories using different versions of the guideline may therefore produce different diagnoses, be it on the presence of, or on the degree of severity of sleep apnea.[205,206] Central sleep apnea also refers to partial or full cessation of breathing during sleep, but is due to reduced or absent respiratory effort instead of obstruction of the airways."

Chapter 2, page 18, after the 2nd paragraph on Sleep-related breathing disorders, include a new paragraph: "Insomnia and Sleep-related breathing disorder often co-occur. Among individuals with a confirmed OSA diagnosis in sleep disorders clinics, the reported prevalence of insomnia ranges from 23.4% to 84.6%.[207] The wide variation in prevalence is primarily attributable to different diagnostic methods for OSA/insomnia and different type of samples between different studies. The prevalence of OSA among those with insomnia is also high, ranging from 30.3% to 60%, and understandably smaller in the general population, 0.6% to 3.5%.[207] Studies have found that COMISA patients are at higher risk of having daytime impairments, lower quality of life, depression, and other psychiatric disorders. [207,208] Patients presenting with COMISA may be more difficult to treat than patients presenting with either of the constituent disorders. Challenges in, and proposed treatment strategies for, COMISA patients are further discussed in a recent review by Sweetman et al. [207]"

Chapter 2.2.3, page 2: "A wide range of sleep disorders produce EDS as a symptom, which in turn has

been associated with health conditions such as nocturia,[209] depression,[171,210] and diabetes,[171] risk factors such as reduced exercise or physical activity,[76] and consequences such as accidents,[77,78] injuries,[79] and reduced academic/professional performances.[80-82] EDS has also been associated with increased likelihood of developing disability,[83,84] and (inconsistently) with increased risk of mortality.[85-88] EDS is especially important for certain subgroups of the population, for example truck/bus drivers,[89] physicians,[90] and judges;[81] whose occupations substantially influence public safety. It was estimated that up to 1 in 3 people in the general American population experience EDS,.[91] with similar findings in Australia.[211]

Sleep deprivation that occurs with most sleep disorders, may disturb the functions of sleep (see subsection 2.2.1), resulting in conditions such as memory impairment,[56] endocrine and metabolic disorders,[59,92] cardiovascular disease,93,94 and poor mental health.[95,96] It was estimated that in 2014, approximately 35% of American adults did not get sufficient sleep (less than 7 hours).[97] In Australia in 2016, 12% people were reported to sleep less than 5.5 hours per day.[211]

The importance of sleep health is becoming increasingly recognised; perhaps due to the growing prevalence of sleep problems[98] and its observed consequences.99,100 More rigorous study on the identification of potential causes and consequences of sleep problems is necessary to help build better prevention strategies and to provide further understanding on the extent to which poor sleep is an important health problem."

Chapter 2, page 46, add to the list of references:

197. Spiegel K, Tasali E, Penev P, Van Cauter E. Brief communication: Sleep curtailment in healthy young men is associated with decreased leptin levels, elevated ghrelin levels, and increased hunger and appetite. Ann Intern Med. 2004;141(11):846-50

198. Nedeltcheva AV, Kilkus JM, Imperial J, Kasza K, Schoeller DA, Penev PD. Sleep curtailment is accompanied by increased intake of calories from snacks. Am J Clin Nutr. 2009;89(1):126-33.

199. Greer SM, Goldstein AN, Walker MP. The impact of sleep deprivation on food desire in the human brain. Nat Commun. 2013;4:2259.

200. Hogenkamp PS, Nilsson E, Nilsson VC, Chapman CD, Vogel H, Lundberg LS, et al. Acute sleep deprivation increases portion size and affects food choice in young men. Psychoneuroendocrinology. 2013;38(9):1668-74.

201. Weiss A, Xu F, Storfer-Isser A, Thomas A, Ievers-Landis CE, Redline S. The association of sleep duration with adolescents' fat and carbohydrate consumption. Sleep. 2010;33(9):1201-9.

202. Shi Z, McEvoy M, Luu J, Attia J. Dietary fat and sleep duration in Chinese men and women. Int J Obes (Lond). 2008;32(12):1835-40.

203. Kleiser C, Wawro N, Stelmach-Mardas M, Boeing H, Gedrich K, Himmerich H, et al. Are sleep duration, midpoint of sleep and sleep quality associated with dietary intake among Bavarian adults? Eur J Clin Nutr. 2017;71(5):631-7.

204. Kant AK, Graubard BI. Association of self-reported sleep duration with eating behaviors of American adults: NHANES 2005-2010. Am J Clin Nutr. 2014;100(3):938-47.

205. Ruehland WR, Rochford PD, O'Donoghue FJ, Pierce RJ, Singh P, Thornton AT. The new AASM criteria for scoring hypopneas: impact on the apnea hypopnea index. Sleep. 2009;32(2):150-7.

206. Nixon GM, Hyde M, Biggs SN, Walter LM, Horne RS, Davey MJ. The impact of recent changes to the respiratory scoring rules in pediatrics. J Clin Sleep Med. 2014;10(11):1217-21.

207. Sweetman AM, Lack LC, Catcheside PG, Antic NA, Chai-Coetzer CL, Smith SS, et al. Developing a successful treatment for co-morbid insomnia and sleep apnoea. Sleep Med Rev. 2017;33:28-38.

208. Lang CJ, Appleton SL, Vakulin A, McEvoy RD, Wittert GA, Martin SA, et al. Co-morbid OSA and insomnia increases depression prevalence and severity in men. Respirology. 2017.

209. Martin SA, Appleton SL, Adams RJ, Taylor AW, Catcheside PG, Vakulin A, et al. Nocturia, Other Lower Urinary Tract Symptoms and Sleep Dysfunction in a Community-Dwelling Cohort of Men. Urology. 2016;97:219-26.

210. Lang CJ, Appleton SL, Vakulin A, McEvoy RD, Vincent AD, Wittert GA, et al. Associations of Undiagnosed Obstructive Sleep Apnea and Excessive Daytime Sleepiness With Depression: An Australian Population Study. J Clin Sleep Med. 2017;13(4):575-82.

211. Adams RJ, Appleton SL, Taylor AW, Gill TK, Lang C, McEvoy RD, et al. Sleep health of Australian adults in 2016: results of the 2016 Sleep Health Foundation national survey. Sleep Health. 2017;3(1):35-42.

Chapter 4, page 72, second paragraph under "Mediators": "OAHI is defined as the number of obstructive apnea and hypopnea events with 4% oxyhemoglobin desaturation level or more, divided by total sleep time. RDI was defined as the number of central or obstructive apnea and hypopnea events with 4% oxyhemoglobin desaturation level or more, divided by total sleep time."

Chapter 4, page 65, insert the following note: "The study in Chapter 4 has undergone substantial revision although the overall message remains unchanged. The full article is published as: Ng WL, Orellana L, Shaw JE, Wong E, Peeters A. The relationship between weight change and daytime sleepiness: the Sleep Heart Health Study. Sleep Med. 2017;36:109-18."